

AHRQ Healthcare Horizon Scanning System – Potential High Impact Interventions Report

Priority Area 03: Cardiovascular Disease

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High Impact report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to effectivehealthcare@ahrq.hhs.gov.

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Contents

Executive Summary	ES-1
Background.....	ES-1
Methods	ES-1
Results.....	ES-2
Discussion.....	ES-4
Anticoagulation Interventions	1
Novel Agents for Anticoagulation.....	2
Arrhythmia Interventions	6
Cardiac Pacing System (Revo) for Patients Who May Require Future Magnetic Resonance Imaging	7
Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD) for Prevention of Sudden Cardiac Arrest.....	10
Heart Failure Interventions.....	13
Autologous Mesenchymal Stem Cell Transplantation (C-Cure) for Treatment of Heart Failure	14
Portable Freedom Driver for In-Home Support of the Total Artificial Heart	17
Hypertension Intervention.....	19
Radiofrequency Ablation Renal Denervation (Symplicity System) for Treatment-Resistant Hypertension.....	20
Myocardial Infarction Intervention	23
Standardized Protocol and Integrated System (RACE Project) for Treatment and Transfer of Patients with ST-Elevation Myocardial Infarction.....	24
Valve and Structural Disorder Interventions.....	28
Off-Label Sildenafil (Viagra) for Improving Pediatric Exercise Tolerance After a Fontan Operation	29
Percutaneous Annuloplasty (Carillon Mitral Contour System) to Treat Functional Mitral Regurgitation	31
Transcatheter Aortic Valve (CoreValve and Sapien) Implantation for Treatment of Severe Aortic Stenosis	34
Transcatheter Mitral Valve Repair (MitraClip) for Treatment of Mitral Regurgitation	38
Transcatheter Pulmonary Valve (Sapien) for Treatment of Congenital Pulmonary Valve Defects....	41
References	44

Figures

Figure 1.	Overall High Impact Potential: Novel pharmacotherapies for anticoagulation.....	4
Figure 2.	Overall High Impact Potential: Cardiac pacing system (Revo) for patients who may require future magnetic resonance imaging	8
Figure 3.	Overall High Impact Potential: Subcutaneous implantable cardioverter-defibrillator (S-ICD) for prevention of sudden cardiac arrest.....	11
Figure 4.	Overall High Impact Potential: Autologous mesenchymal stem cell transplantation (C-Cure) for treatment of heart failure.....	15
Figure 5.	Overall High Impact Potential: Portable driver system (Freedom Driver) for total artificial heart	18
Figure 6.	Overall High Impact Potential: Radiofrequency ablation renal denervation (Symplicity System) for treatment-resistant hypertension	21
Figure 7.	Overall High Impact Potential: Standardized protocol and integrated system (RACE Project) for treatment and transfer of patients with ST-elevation myocardial infarction	26
Figure 8.	Overall High Impact Potential: Off-label sildenafil (Viagra) for improving pediatric exercise tolerance post-Fontan operation	30
Figure 9.	Overall High Impact Potential: Percutaneous annuloplasty (Carillon Mitral Contour System) to treat functional mitral regurgitation.....	32
Figure 10.	Overall High Impact Potential: Transcatheter aortic valves (CoreValve and Sapien) implantation for treatment of severe aortic stenosis	36
Figure 11.	Overall High Impact Potential: Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation	39
Figure 12.	Overall High Impact Potential: Transcatheter pulmonary valves (Sapien) for treatment of congenital pulmonary valve defects	42

Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identifying new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 7 years out on the horizon and then to follow them for up to 2 years after initial entry into the health care system. Since that implementation, more than 11,000 leads about topics have resulted in identification and tracking of more than 900 topics across the 14 AHRQ priority areas and one cross-cutting area.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0–4 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COI). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the potential high impact range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as potential high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

Results

The table below lists the 32 topics for which (1) preliminary phase III data for drugs or phase II or III data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled before April 15, 2012, in this priority area; *and* (3) we received six to eight sets of comments from experts between February 2011 and April 26, 2012. (Ninety-three topics in this priority area were being tracked in the system as of May 2012.) For purposes of the Potential High Impact Interventions Report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). We present 12 summaries on 16 topics (indicated below by an asterisk) that emerged as having potential for high impact on the basis of experts’ comments and their assessment of potential impact. The material on interventions in this Executive Summary and report is organized alphabetically by disease state and interventions within that disease state. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 03: Cardiovascular

Topic	High Impact Potential
1. Anacetrapib for treatment of dyslipidemia	No high-impact potential at this time
2. Apo-B synthesis inhibitor (mipomersen) for treatment of familial hypercholesterolemia	No high-impact potential at this time
3. Baroreflex stimulation for treatment of drug-resistant hypertension	No high-impact potential at this time
4. Cardiac contractility (Optimizer III) modulation for palliation of heart failure symptoms	No high-impact potential at this time
5. *Cardiac pacing system (Revo) for patients who may require future magnetic resonance imaging	Lower range of high impact
6. *Portable Freedom Driver for In-Home Support of Total Artificial Heart	Lower range of high impact
7. Endovascular pipeline embolization device (PED) for treatment of brain aneurysms	No high-impact potential at this time
8. *Factor Xa inhibitor (apixaban) for anticoagulation	Moderately high
9. *Factor Xa inhibitor (edoxaban) for anticoagulation	Moderately high

Topic	High Impact Potential
10. *Factor Xa inhibitor (rivaroxaban) for anticoagulation	Moderately high
11. Implantable cardiac monitor (AngelMed Guardian System) to detect impending myocardial infarction	No high-impact potential at this time
12. Left ventricular end diastolic pressure-based hydration for renal protection during coronary angiography	No high-impact potential at this time
13. Low-dose tPA for treatment of intraventricular hemorrhage	No high-impact potential at this time
14. Magnetically levitated centrifugal pump ventricular-assist device (DuraHeart) as bridge to transplantation for end-stage heart failure	No high-impact potential at this time
15. Magnetically levitated centrifugal pump ventricular-assist device (HeartWare) as bridge to transplantation for end-stage heart failure	No high-impact potential at this time
16. Magnetically levitated centrifugal pump ventricular-assist device (HeartWare) as destination therapy for end-stage heart failure	No high-impact potential at this time
17. MTP inhibitor (lomitapide) for treatment of homozygous familial hypercholesterolemia	No high-impact potential at this time
18. Off-label minocycline with tPA for treatment of stroke	No high-impact potential at this time
19. *Off-label sildenafil (Viagra) for improvement in pediatric exercise tolerance post-Fontan operation	Lower range of high impact
20. *Percutaneous annuloplasty (Carillon Mitral Contour System) to treat functional mitral regurgitation	Moderately high
21. *Radiofrequency ablation (Symplicity System) for renal denervation for treatment-resistant hypertension	Lower range of high impact
22. Robotic system (CorPath 200) for remotely controlled percutaneous coronary intervention	No high-impact potential at this time
23. School-wide electrocardiogram screening (Young Hearts for Life) for cardiac abnormalities in students	No high-impact potential at this time
24. *Standardized protocol and integrated system (RACE Project) for treatment and transfer of patients with ST-elevation myocardial infarction	High
25. *Stem cell therapy (C-Cure) for treatment of heart failure	High
26. *Subcutaneous implantable cardioverter defibrillator (S-ICD) for cardiomyopathy	Lower range of high impact
27. *Thrombin inhibitor (dabigatran) for anticoagulation	Moderately high
28. *Transcatheter aortic valve implantation (CoreValve) for treatment of severe aortic stenosis	High
29. *Transcatheter aortic valve implantation (Sapien) for treatment of severe aortic stenosis	High
30. *Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation	High
31. *Transcatheter pulmonary valve (Sapien) for treatment of pulmonary valve congenital defects	Lower range of high impact
32. Vagus nerve stimulation for treatment of congestive heart failure	No high-impact potential at this time

Discussion

Research activity in all disease areas of the cardiovascular priority area is robust and addresses both novel and incremental innovations that could affect patient outcomes, shift care models, affect costs, and affect delivery of care.

Anticoagulation

Anticoagulation therapy is needed for a number of clinical conditions, such as venous thromboembolism (VTE). VTE can manifest as either deep vein thrombosis (DVT), which occurs when blood coagulates to form a thrombus in one of the deep veins, or pulmonary embolism (PE), which occurs when a deep vein thrombus breaks off and migrates to the lungs' arterial supply, causing potentially life-threatening ventilation perfusion defect and cardiac strain. According to the American Heart Association (AHA), about two-thirds of patients with VTE develop DVT alone, and a third also develop PE. The estimated annual incidence in the United States for DVT and PE is 0.1%, and between 350,000 and 600,000 people in the United States have DVT and PE each year. About 30% of patients newly diagnosed with VTE die within 30 days (primarily from PE), and 30% of patients develop recurring VTE within 10 years. An estimated 100,000 deaths each year are directly or indirectly related to DVT and PE. AHA and the Surgeon General's office say that although the contribution of DVT and PE to mortality and medical costs is high, limited data have been gathered about VTE's total economic costs. Thrombosis can also cause stroke, and risk factors for stroke include atrial fibrillation (AF), the most common type of cardiac arrhythmia. AF is characterized by abnormal electrical impulses that cause the heart's atria to beat improperly and out of sequence. During an AF episode, the atria cannot pump blood effectively to the ventricles, and pooled blood within the atria may form clots that can travel to the brain and cause ischemia and/or stroke. In the United States, AF affects more than 2.2 million people and is associated with 15% to 25% of all strokes. AF prevalence increases with age: nearly 4% of Americans older than 60 years and 8% older than 80 years have this condition, according to the Framingham Heart Study. AF prevalence varies by ethnicity, with the highest rates in Caucasian (5.7%), Native American/Alaskan (5.4%), and Pacific Islander (5.2%) male patients, and lower rates in Asian (3.6%), African-American (3.4%), and Hispanic (3.0%) male patients, according to Borzecki and colleagues, Department of Veterans Affairs' Center for Health, Quality, Outcomes and Economic Research (2008). AF incidence is less than 0.1% per year in Americans aged 40 years or younger and between 1.5% and 2.0% in those aged 80 years or older, according to AF-management guidelines. Experts commenting on anticoagulation topics identified four drugs that they thought had potential for high impact.

Novel Agents for Anticoagulation

- **Key Facts:** Anticoagulation therapy is regarded as an important and unavoidable component in managing patients with, or at risk for DVT, PE, and stroke. These patients include those who have undergone orthopedic surgeries such as knee or hip replacement. However, anticoagulation agents, such as warfarin, heparin, low-molecular-weight heparin, and fondaparinux, are characterized by many limitations, including unpredictable anticoagulation profiles, undesirable routes of administration, need for frequent laboratory monitoring of clotting parameters and frequent dose adjustments, unpredictable dose-response relationships, potential for drug and dietary interactions, and risk for bleeding. The

newer agents, low-molecular-weight heparin and fondaparinux, a pentasaccharide, require parenteral administration, are more expensive than warfarin, and might not be usable in patients with renal or hepatic dysfunction.

In light of these shortcomings, drug manufacturers have recently developed novel anticoagulation agents that might not have the limitations that are characteristic of older agents. These new agents include an oral direct thrombin inhibitor and three factor Xa (FXa) inhibitors.

Novel agents, two of which have been approved for marketing in the United States (dabigatran and rivaroxaban), have been recently developed to address some of these limitations. Agents in development include apixaban and edoxaban, which are FXa inhibitors like the recently approved rivaroxaban. The reported average wholesale price (AWP) of the FXa inhibitor rivaroxaban is \$8.10 per 10 mg tablet, which is a typical daily dosage after knee or hip surgery, although dosage can also be 20 mg/day depending on the patient and clinical circumstance. Thus, the AWP for a month supply of 30 tablets (10 mg) would be \$243. This pricing can serve as a benchmark for how the other FXa agents might be priced.

- **Key Expert Comments:** Experts commenting on these drugs thought that these agents have significant potential to improve patients' quality of life and reduce burdens on the health care system by obviating the need for ongoing laboratory monitoring, dose adjustments, and dietary restrictions. Because the drugs in this class are self-administered oral pills, they are expected to be easily adopted into current care models, according to these experts.
- **Potential for High Impact:** Moderate range of high impact

Arrhythmia

According to AHA, arrhythmias (abnormal heartbeats) are a major source of cardiovascular-related morbidity and mortality. Ventricular tachycardia (rapid heartbeat) and ventricular fibrillation (unsynchronized heartbeat) reduce the heart's pumping ability and can cause collapse, cardiac arrest, and sudden death. These conditions are believed to contribute to the more than 400,000 deaths from sudden cardiac arrest (SCA) that occur in the United States each year. Numerous drugs and implantable devices exist to treat arrhythmia. Unfortunately, drugs for rhythm and rate control carry significant risks of adverse events, and available implantable devices often contraindicate certain procedures (e.g., magnetic resonance imaging [MRI]). Therefore, a significant unmet need exists for better and safer treatments for patients with various forms of cardiac arrhythmia. Experts highlighted two devices that could be of potentially high impact in treating arrhythmia.

Cardiac Pacing System (Revo) for Patients Who May Require Future Magnetic Resonance Imaging

- **Key Facts:** To address concerns about pacemaker-compatible MRI imaging, a new pacemaker was developed and approved for marketing in February 2011. The Revo MRI™ Sure Scan® pacing system (Medtronic, Inc., Minneapolis, MN) is a dual-lead electronic, implantable, cardiac pacemaker engineered to allow patients to safely undergo MRI scans under specific conditions. The U.S. Food and Drug Administration (FDA) approved the device as “MR-conditional,” meaning that it can be used in an MRI environment under certain conditions according to the type of MRI scanner and scanner settings. A phase III trial of 464 patients reported that no MRI-related complications—which include sustained

ventricular arrhythmias, pacemaker inhibition or output failures, electrical resets, or other pacemaker malfunctions—occurred during or after MRI procedures. The list price for the Revo is \$13,000, according to Medtronic. Hospitals and group purchasing organizations typically negotiate significant discounts on such devices.

- **Key Expert Comments:** Experts commenting on this new device were divided about its potential impact. On one hand, experts agreed that having the capability to conduct MRI scans in patients with pacemakers is important. However, experts also noted that novel protocols are being investigated to determine whether conventional pacemakers can be used in this capacity, which could obviate the need for the Revo. Although experts thought acceptance of the device would be high by both clinicians and patients, the device's cost, training requirements, and lack of data might temper its diffusion.
- **Potential for High Impact:** Lower range of high impact

Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD) for Prevention of Sudden Cardiac Arrest

- **Key Facts:** The standard available implantable cardioverter-defibrillators (ICDs) that are intended to prevent SCA have been associated with lead failure that can generate unnecessary shocks or fail to provide necessary shocks. When faulty leads are removed and replaced, substantial morbidity and mortality has occurred. The S-ICD[®] System (Cameron Health, Inc., San Clemente, CA, which will be acquired by Boston Scientific Corp., Natick, MA, in late 2012) in late-phase development is a subcutaneous ICD that is intended to be minimally invasive and does not require electrode leads to be placed in or on the heart. Furthermore, the device does not require imaging equipment for placement because the system components are designed to be positioned using only anatomic landmarks. The company submitted its premarket approval (PMA) application to FDA in December 2011, and in April 2012, an FDA Circulatory System Devices advisory panel recommended approval of the device.
- **Key Expert Comments:** Experts were somewhat optimistic that this intervention might have some potential to improve patient health outcomes by reducing complications associated with lead-based ICDs and associated secondary surgeries that carry a high risk of morbidity and some mortality, although this optimism was diluted by a couple of experts who suggested that this device's limited pacing capabilities would temper its diffusion. Because the implantation procedure requires fewer resources and can be performed in an outpatient setting, this intervention could shift care delivery to a less invasive setting and result in shorter hospital stays.
- **Potential for High Impact:** Lower range of high impact

Heart Failure

Heart failure (HF), a debilitating condition that adversely affects quality of life as well as life expectancy, can develop from any condition that overloads, damages, or reduces the efficiency of the heart muscle, impairing the ventricles' ability to fill with or eject blood. According to AHA, about 5.7 million adults aged 20 years or older in the United States were living with HF in 2009. Those surviving a heart attack are the most at risk. AHA estimates that for the U.S. population 65 years of age or older, the incidence of HF is about 10 per 1,000 people. Nearly 550,000 new cases of HF occur each year. In 2005 (the most recent year for which mortality statistics are available),

more than 292,000 patients died in the United States with a prior diagnosis of HF; it was listed as the underlying cause in nearly 59,000 of the deaths and a contributing (secondary) factor in the remaining cases. The prevalence of HF has increased during the past 20 years, and the number of patients who progress to end-stage HF is expected to grow because of increased survival in patients with coronary artery disease, an increased population of aging patients, and significant advances in the control of other potentially lethal diseases. Because of the clear unmet need for effective therapies for HF and its underlying cause, many new drugs, biologics, and devices are under study for treating patients with HF. Experts commenting on topics on HF identified one biologic and one device they thought had potential for high impact.

Autologous Mesenchymal Stem Cell Therapy (C-Cure)

- **Key Facts:** Available HF treatments are unable to reverse the disease process, and mortality from HF remains high, even when optimally treated. Also, determining which drugs will work in which patients is a challenge, addressed by trial and error with medication regimens. A significant unmet need exists for disease-modifying therapies for this condition. C-Cure[®] (Cardio3 Biosciences, S.A., Mont-Saint-Guibert, Belgium) is a bone-marrow-derived, cardiopoietic (i.e., having cardiac cell-generating potential), mesenchymal stem cell therapy that the manufacturer claims can potentially regenerate damaged heart muscle tissue without risk of rejection. The therapy involves harvesting mesenchymal cells from the patient's bone marrow, treating the cells with growth factors (a "cardiopoietic cocktail"), and then injecting the cells into the patient's heart. The cocktail includes transforming growth factor-beta1, bone morphogenetic protein-4, activin A, retinoic acid, insulin-like growth factor-1, fibroblast growth factor-2, alpha-thrombin, and interleukin-6. The company claims that treatment with these proteins can transform mesenchymal (undifferentiated) stem cells into cardiac progenitor cells to replicate natural cardiogenesis, without modifying the genome of the cell. The cardiac progenitor cells are designed to behave identically to cells lost during progression of HF, and they purportedly regenerate damaged heart muscle without risk of rejection. The therapy entered phase III trials the latter half of 2011 based on promising phase II results in which patients were reported to have shown an 18.1% improvement in left-ventricular ejection fraction.
- **Key Expert Comments:** Some experts providing comments were skeptical about this intervention's potential efficacy pending larger and longer-term trial results, but experts generally agreed that this intervention might have dramatic effects on the health care system, should its efficacy be proven. Furthermore, experts considered the need for disease-modifying HF therapies to be extremely important. As a potentially disease-modifying therapy for HF, experts commented, this therapy has the potential to significantly affect certain parameters of the health care system, including the costs of treating HF, and to establish a treatment paradigm that treats the disease instead of the disease's symptoms.
- **Potential for High Impact:** High

Portable Freedom Driver for In-Home Support of the Total Artificial Heart

- **Key Facts:** The Freedom[®] Driver System (SynCardia Systems, Inc., Tucson, AZ) is a wearable, pneumatic, portable driver under development to enable at-home support for the temporary Total Artificial Heart [TAH-t] (SynCardia) in patients awaiting a heart transplant. The TAH-t, approved as a bridge to transplantation by FDA in October 2004, is indicated

for use in cardiac-transplant-eligible patients at risk of imminent death from nonreversible biventricular failure. The TAH-t is powered by a conventional pneumatic driver system, which is a large and cumbersome device that requires patients to remain hospitalized while awaiting a donor heart. A portable driver system that might allow patients to be discharged from the hospital while awaiting a suitable donor heart would address a significant unmet need for the relatively small number of patients in this patient population. The Freedom Driver System weighs 13.5 lb and is carried in a backpack or shoulder bag. The driver is powered by two onboard batteries that can be recharged with an automobile adapter or a standard electrical outlet. As with conventional, large, hospital-based pneumatic driver systems, the Freedom driver is connected to the implantable TAH-t by a flexible pneumatic driveline that passes through the patient's skin in the left chest just below the ribs. The driver flashes a light or sounds an alarm when the system requires the user's attention. A clinical trial of the driver is ongoing.

- **Key Expert Comments:** Although this intervention is expected to have an impact on quality of life for patients and health care costs associated with lengthy hospital stays, the patient population for which this device is intended is small, which tempers its potential impact on the health care system. However, experts thought that shifting care from the inpatient to the outpatient setting could be an important effect of this intervention.
- **Potential for High Impact:** Lower range of high impact

Hypertension

Hypertension, or high blood pressure, affects about one-third of the adult population in the United States and has long been described as the “silent killer,” because it often shows no specific symptoms. However, more pronounced symptoms are associated with severe or long-term hypertension and include severe headache, dizziness or confusion, nausea, fatigue, blurred vision, chest pain, difficulty breathing, irregular heartbeat, and blood in the urine. According to AHA, about 76.4 million people in the United States have hypertension. National health surveys from both highly industrialized and developing nations suggest that hypertension is effectively managed in only 11.2% of cases. Hypertension was the primary cause of 61,005 deaths in the United States in 2008, the most recent year for which statistics were available, according to AHA and the American Stroke Association. Experts commenting on hypertension topics identified one procedure they thought had potential for high impact.

Radiofrequency Ablation (Symplicity System) for Renal Denervation for Treatment-Resistant Hypertension

- **Key Facts:** Lowering high blood pressure has been associated with significantly lower rates of stroke, heart attack, and HF, and inadequately controlled hypertension remains a problem for a growing number of people. The Symplicity™ Catheter System (Medtronic) allows a physician to apply radiofrequency energy to ablate the renal nerves from within the renal artery without adversely affecting other nerves in the abdomen, pelvis, or lower extremities. The minimally invasive procedure takes about 40 minutes to perform; according to the company, physicians perform the renal denervation procedure in a catheterization laboratory using standard interventional techniques similar to those used for renal stent implantation. In July 2011, FDA approved a trial protocol for conduct of SYMPPLICITY HTN-3, a randomized, controlled trial in the United States.

- **Key Expert Comments:** Experts commenting on this intervention agreed that it has the potential to fill an important gap in treatment of hypertension and would likely be somewhat accepted by clinicians and patients. However, this intervention's potential impact is tempered by its lack of longer-term outcomes data, and the likelihood that it would be easily incorporated into existing health care infrastructure.
- **Potential for High Impact:** Lower range of high impact

Myocardial Infarction

Myocardial infarction (MI), or heart attack, is caused by one or more blockages (usually by a blood clot) of the coronary arteries or their major branches, leading to ischemia in heart muscle tissue. During an ischemic event, heart muscle tissue can be irreparably damaged as cells cease functioning properly, potentially leading to the patient's death if the blockage is not cleared or bypassed. In coronary arteries that are significantly narrowed by plaque, events that cause coronary constriction (e.g., strenuous exercise, severe stress) can also cause MI. Modifiable risk factors for MI include smoking (or other tobacco use), diabetes mellitus, hypertension, hypercholesterolemia and hypertriglyceridemia, dyslipidemia, obesity, sedentary lifestyle, psychosocial stress, poor oral hygiene, and Type A personality. Nonmodifiable MI risk factors include age, sex, family history of premature coronary heart disease, and male-pattern baldness. According to AHA, the average age for a patient's first MI is 64.5 years for males and 70.3 years for females. AHA predicts that about 785,000 new and 470,000 recurrent MIs will occur in 2012 in the United States plus an additional 195,000 "silent" (nonsymptomatic) MIs. About 15% of patients experiencing an MI will die from the event, according to AHA. Experts commenting on MI topics identified one care delivery innovation that they thought could have high impact.

Standardized Protocol and Integrated System (RACE Project) for Treatment and Transfer of Patients with ST-Elevation Myocardial Infarction

- **Key Facts:** A sizable proportion of patients with ST-elevation myocardial infarction do not receive reperfusion therapy in a timely manner, resulting in suboptimal health outcomes. This unmet need is due to several systemic factors, which the RACE project purports to address. The RACE quality improvement project was developed in North Carolina to align health professionals and organizations to overcome systematic barriers, decrease delays in administering reperfusion therapy, increase the frequency with which reperfusion is provided to eligible patients, and improve processes of care. Participants in the project use an intake tool to evaluate current practice at a hospital, then use that information along with hospital-specific data to determine appropriate system recommendations. Recommendations occur at several levels: emergency medical services, the emergency department, interhospital transportation, primary percutaneous coronary intervention center communication, etc. Thus far, the RACE project has been implemented in 68 hospitals in North Carolina and is intended to be used as a model for other statewide systems.
- **Key Expert Comments:** Given the evidence base that supports timely percutaneous coronary intervention, and the large proportion of patients who are still not receiving it, experts agree that this intervention has the potential to address an important unmet need in the health care system. Besides disrupting existing health care infrastructure and patient management models, experts thought, this intervention will also improve patient health

outcomes and improve health disparities, particularly for rural populations. Although clinicians and patients are expected to accept this initiative, experts thought that issues of reimbursement and the potential for revenue losses at hospitals will need to be addressed before wide adoption will be possible.

- **Potential for High Impact:** High

Valve and Structural Disorders

This section includes topics that purport to address unmet needs for certain disorders of heart valves and one disorder associated with a ventricle malformation.

Mitral regurgitation (MR) is defined broadly as a backward flow of blood from the heart's left ventricle into the left atrium during contraction. MR can be divided into two major categories: primary, or organic MR and secondary, or functional MR (FMR). FMR is associated with poor long-term survival, and its presence in patients with ischemic and dilated cardiomyopathy is an independent risk factor for cardiovascular morbidity and mortality. Research has shown that 1-year mortality is 40% for patients with severe FMR, 17% for patients with moderate FMR, and 10% for patients with mild FMR, according to Schmitto and colleagues, Harvard Medical School (2010). Significant MR occurs in an estimated 1% to 2% (about 4 million) of the U.S. population. More than 250,000 cases of significant MR are diagnosed each year in the United States and about 50,000 people undergo some type of surgery for the disease, according to one manufacturer in the field.

Aortic valve stenosis is a narrowing that obstructs normal blood flow through the aortic valve, the most likely of the heart's four valves to fail because of disease. Severe, untreated aortic valve stenosis can eventually lead to HF or SCA. In the United States, about 29% of people aged 65 years or older and 37% of people aged 75 years or older have aortic sclerosis, a precursor condition to aortic stenosis characterized by mild thickening or calcification or both of the aortic valve without restricted leaflet motion, according to researchers. About 1% to 2% of the population is living with a bicuspid aortic valve, a congenital defect in which the aortic valve develops two instead of three normal valve leaflets. Half of this population will develop aortic stenosis, according to Novaro of the Cleveland Clinic (2011).

A stenotic or regurgitant pulmonary valve, associated with several congenital disorders, can affect ventricular function and lead to shortness of breath, fatigue, light-headedness, weakness, and exercise intolerance. These conditions can also cause heart palpitations and chest pain. AHA says that in the United States, about 1% of all infants born alive have a congenital heart defect. About 22% of those infants have a defect affecting the flow of blood from the right ventricle to the pulmonary artery, one manufacturer asserts.

The Fontan operation is a palliative surgical procedure that is primarily used in patients who have complex cardiac malformations that leave a single anatomical functional ventricle in the heart. In these cases, the circulation must be surgically reconfigured to maximize the efficiency of the working ventricle without overburdening it. Without surgical intervention, only 42% of children with a single ventricle will survive to 1 year of age, according to Brown, Harvard Medical School (2011). An estimated 1,200 Fontan operations are performed annually in the United States, according to Chin and colleagues, Children's Hospital of Philadelphia (2010).

Experts commenting on topics in this area identified four devices and one drug that they thought could have high impact.

Off-label Sildenafil (Viagra) for Improving Pediatric Exercise Tolerance After a Fontan Operation

- **Key Facts:** After a Fontan operation, patients often experience compromised exercise capacity, due to the inability of the reconstructed heart to keep up with the increased metabolic demand associated with exercise. No medical therapies have demonstrated a benefit in improving exercise tolerance in patients who have undergone a Fontan operation, although exercise training can improve aerobic capacity in some patients. Therefore, an unmet need exists for effective interventions that will improve patients' exercise capacity, which, in turn, can improve quality of life. Sildenafil is an FDA-approved phosphodiesterase type 5 inhibitor that is known to exert a potent selective vasodilatory effect on the pulmonary vasculature, thereby lowering resistance in lung vessels and improving blood flow. In patients with pulmonary arterial hypertension, a condition characterized by abnormally high lung resistance and a resulting inability of the heart to keep up with metabolic demands, sildenafil has been shown to improve exercise performance. Because it is known that patients who have undergone a Fontan operation also manifest limited cardiac output due to lung resistance, academic and clinical researchers are now investigating the off-label use of sildenafil as a means of improving exercise capacity in these patients. Researchers speculate that if the drug is effective, treated patients will have an improved efficiency of blood flow through the lungs and, as a result, improved cardiac output. These changes might offer patients the benefit of diminished symptoms; increased energy; an increased ability to walk, run, or play sports; and an improved quality of life. In the most recent clinical trial investigating the off-label use of sildenafil in this population, 28 children and young adults with Fontan circulation were randomly assigned to receive placebo or sildenafil (20 mg three times daily) for 6 weeks, then after a 6-week washout, crossed over for an additional 6 weeks. One clinical trial has been completed, and one clinical trial is ongoing.
- **Key Expert Comments:** Experts unanimously agreed that the unmet need this intervention purports to address is important, given the quality of life and health-related effects of Fontan circulation. Experts also agreed that this intervention is likely to meet this need, in light of sildenafil's mechanism of action. However, because the target patient population is small in number, the drug can be administered easily, and the high cost of the off-label product might prohibit uptake, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.
- **Potential for High Impact:** Lower range of high impact

Percutaneous Annuloplasty (Carillon Mitral Contour System) to Treat Functional Mitral Regurgitation

- **Key Facts:** Open surgical repair of the mitral valve, known as "mitral annuloplasty," is considered the gold standard treatment for MR. Percutaneous annuloplasty is a new minimally invasive surgical approach intended to achieve the same therapeutic result, using a catheter-based technique. The Carillon[®] Mitral Contour System[™] (Cardiac Dimensions, Inc., Kirkland, WA) comprises a thin, flexible, metal bridge or tether with a self-expanding anchor at each end. The device is delivered to the coronary sinus by a catheter inserted in the jugular vein at the neck. The physician places tension on the delivery catheter to reshape the mitral annulus sufficiently to reduce the degree of MR by squeezing the mitral leaflets

together to close the gap that might have developed due to heart enlargement. Two international trials are ongoing. The device is available in the United States only under investigational device exemption status in clinical trials. The device was Conformité Européenne (CE) marked for marketing in Europe in October 2011, and the company anticipated a product launch in Europe in early 2012.

- **Key Expert Comments:** Experts commenting on this intervention generally agreed that the unmet need for a less invasive alternative to surgical mitral valve repair is important. However, experts' uncertainty about the Carillon device's long-term safety and efficacy profiles indicate that more data are needed to determine whether this approach will fulfill its potential. Should the device be proven safe and effective, experts thought, it might reduce recovery time and hospital length of stay for patients; they also thought that the device would be readily adopted by clinicians and patients.
- **Potential for High Impact:** Moderate range of high impact

Transcatheter Aortic Valve (CoreValve, Sapien) Implantation for Treatment of Severe Aortic Stenosis

- **Key Facts:** New minimally invasive approaches could make available the therapeutic benefit of aortic valve replacement to patients with aortic stenosis who are not candidates for open-heart valve surgery because of high surgical risk. One system is in development (CoreValve[®]), while the other (Sapien) was recently approved by FDA.

Medtronic is developing the aortic CoreValve System, which features a porcine pericardial tissue valve mounted in a self-expanding, hourglass-shaped, nitinol-alloy mesh frame. The bioprosthetic valve is deployed using an 18-French diameter delivery catheter with a set of disposable catheter-loading components in a procedure that lasts 1–3 hours and requires a 3–5 day hospital stay. Medtronic received an investigational device exemption designation for its CoreValve trial from FDA in October 2010 and trials are under way. In 2012, the U.S. Centers for Medicare & Medicaid Services (CMS) released a national coverage determination for these procedures, stating that under certain circumstances, it will reimburse for them.

Edwards Lifesciences, LLC, Irvine, CA, developed the Sapien Transcatheter Heart Valve (THV), which features a bovine pericardial tissue aortic valve affixed within a balloon-expandable, cobalt-chromium alloy frame. The bioprosthetic valve is available in 23 and 26 mm lengths. The company has developed delivery systems for implanting the valve using either a transfemoral or transapical approach, but only the transfemoral approach has been evaluated by FDA for marketing approval at this time. The procedure is conducted in 1–3 hours, and the average hospital stay for a patient undergoing the implant procedure is 2–6 days. In November 2011, FDA approved the Sapien THV for transfemoral delivery for treating patients with severe, symptomatic, aortic stenosis who have been determined by a cardiac surgeon to be ineligible for open aortic valve replacement and in whom existing comorbidities would not preclude the expected benefit from the procedure. FDA requested, as conditions of approval, two substantial post-approval studies. One study will conduct long-term followup on patients already enrolled in the PARTNER trial, and the second study will track new U.S. patients given the valve. In May 2012, CMS released a national coverage determination stating that CMS “covers transcatheter aortic valve replacement (TAVR) under Coverage with Evidence Development (CED)” when it the procedure is used

for “the treatment of symptomatic aortic valve stenosis when furnished according to an FDA approved indication” and when certain conditions are met, including the required credentials and experience of the facilities and surgeons who can perform the procedure.

The Sapien valve device costs a reported \$30,000. In November 2011, investigators reported a cost-effectiveness comparison between TAVR and open-heart aortic valve replacement among Cohort A (high-risk) patients in the PARTNER trial. The authors found that for transfemoral TAVR, procedural costs were substantially higher than those for open-heart aortic valve replacement. However, overall treatment costs for the entire index hospitalization were \$2,500 lower for transfemoral TAVR than for open surgery, largely because of a shorter hospital stay associated with the former.

- **Key Expert Comments:** Experts commenting on this intervention agreed that it would offer an important and likely safe and effective new treatment modality for patients who have no other medical or surgical treatment option. Experts thought that this intervention would improve patient health outcomes, and they thought an increase in patient volume and a shift in care setting (from outpatient to inpatient) would be seen as this intervention diffuses. Experts offered diverging opinions on whether this intervention would be particularly disruptive to health care infrastructure but agreed that the intervention has the potential to both increase (in the short term) and decrease (in the long term) health care costs.
- **Potential for High Impact:** High

Transcatheter Mitral Valve Repair (MitraClip) for Treatment of Mitral Regurgitation

- **Key Facts:** Transcatheter mitral valve repair with the MitraClip® device (Abbott Laboratories, Abbott Park, IL) is intended to simulate the functional effects achieved by the standard open-surgery repair procedure used for treating MR. In the standard procedure, a surgeon sutures together the edges of the two opposing mitral valve leaflets at the center of the valve opening, leaving two smaller openings on either side that close more completely than a single large opening. In a MitraClip procedure, the physician uses a transcatheter approach in which a two-armed, flexible metal clip covered in polyester fabric is used, rather than the sutures used during open surgery. Researchers reported on outcomes of 279 patients from the EVEREST II randomized, controlled trial, stating a clinical success rate of 51.7 percent for patients treated with the MitraClip compared with a clinical success rate of 66.3 percent for surgery patients ($p=0.04$) at 2-year followup. The device is in phase III trials in the United States. It received the Conformité Européene (CE) mark for marketing in Europe in 2008 for use as a nonsurgical option in patients with severe MR.
- **Key Expert Comments:** Overall, experts agreed this procedure has the potential to substantially affect many parameters of the health care system, changing care models, increasing infrastructure and staffing requirements, shifting care setting, and requiring substantial clinician training; they were split on whether it would increase or decrease costs. Although several experts noted the need for longer-term safety data, experts generally believe that this device has the potential to meet the need for minimally invasive interventions for treating MR.
- **Potential for High Impact:** High

Transcatheter Pulmonary Valve (Sapien) for Treatment of Congenital Pulmonary Valve Defects

- **Key Facts:** Minimally invasive transcatheter pulmonary valves are a new technology intended as a temporary solution to treat congenital pulmonary valve defects and reduce the number of open-heart surgeries these patients must undergo over a lifetime. The Melody[®] transcatheter valve (Medtronic) received FDA approval under humanitarian device exemption status (i.e., affects 4,000 or fewer patients per year) in early 2010 as the first valve available in the United States for this purpose, but this valve only serves patients with certain valve conduit sizes. The Sapien transcatheter pulmonic valve system (Edwards Lifesciences) is intended to serve a patient population with larger failed conduits than the Melody system because the valve (23 and 26 mm) and delivery systems (22 and 24 French diameter) are available in larger sizes. In the United States, Edwards Lifesciences aims to apply for humanitarian device exemption status from FDA, and clinical trials are ongoing. Pricing for the device is not available; however, Medtronic's Melody transcatheter valve system might provide a benchmark for the price of the Sapien system. The Melody valve and delivery device costs \$30,500, with procedural costs totaling about \$50,000. The Sapien device received Conformité Européene (CE) mark approval for the pulmonic valve in May 2010.
- **Key Expert Comments:** Although experts were optimistic about this intervention's ability to meet the need it purports to address, experts believe that the introduction and wide acceptance of the Melody valve somewhat tempers the Sapien valve's potential for high impact, as does the small number of patients in the intended patient population. Because the intervention could reduce or delay the need for open-heart surgeries, this device could have a significant impact on multiple health system parameters by enabling patients to avoid open-heart surgery, moving a procedure from the surgical suite to catheter laboratory setting, reducing cost, and improving patient outcomes, but only for those patients who are not only served by the Melody valve.
- **Potential for High Impact:** Lower range of high impact

Anticoagulation Interventions

Novel Agents for Anticoagulation

For patients at risk of stroke due to atrial fibrillation (AF) or in whom risk or presence of venous thromboembolism (VTE) has been diagnosed, anticoagulation therapy is an important and unavoidable aspect of patient management.^{1,2} Although several anticoagulation agents (e.g., warfarin, unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], fondaparinux) are available, each of these is associated with limitations.¹⁻³ Limitations of warfarin, a vitamin K antagonist, and UFH include narrow therapeutic windows, unpredictable dose-response relationships, a need for laboratory monitoring, potential for drug and dietary interactions, and risk for bleeding.^{3,4} Newer agents LMWH and fondaparinux, a pentasaccharide, require parenteral administration, are more expensive than warfarin, and may not be usable in patients with renal or hepatic dysfunction.^{3,4}

In light of these shortcomings, drug manufacturers have recently developed novel anticoagulation agents that may not have the limitations that are characteristic of older agents.^{3,4} These new agents include an oral direct thrombin inhibitor and three factor Xa (FXa) inhibitors.

Dabigatran (Pradaxa[®], Boehringer Ingelheim GmbH, Ingelheim, Germany) is an oral direct thrombin inhibitor that was approved by the U.S. Food and Drug Administration (FDA) in 2010 for stroke risk reduction in patients with nonvalvular AF and it is also being investigated for other indications, such as preventing and treating VTE.⁵ Unlike other anticoagulants, dabigatran exerts its effects on thrombin, an element of the coagulation cascade.⁶ Whereas previous anticoagulants work by inhibiting thrombin generation or indirectly inhibiting thrombin, dabigatran prevents and disrupts blood clots by directly inhibiting both free and clot-bound thrombin in a reversible manner, preventing thrombin from converting fibrinogen to fibrin, one of the main components of blood clots.⁷⁻⁹ Investigators believe that because of this mechanism of action, dabigatran can be administered as a fixed oral dose, with a rapid onset of action, and without the need for regular monitoring.⁶ Additionally, because dabigatran is not metabolized through the liver, the agent has a low potential for food and drug interactions, researchers believe.⁶ Dosing of dabigatran depends on renal function, which is measured by creatinine clearance. According to FDA-approved prescribing information for patients with AF, individuals with healthy kidneys are recommended the dose of 150 mg orally twice daily, with or without food.¹⁰ For patients with lower creatinine clearance, the recommended dose is 75 mg twice daily; dosing information was not provided for patients with very low creatinine clearance or who are on dialysis.¹⁰

FXa is a serine protease that converts prothrombin to thrombin and is one of the final elements in the coagulation cascade.^{11,12} Direct FXa inhibitors act by specifically binding to the active site of FXa, preventing FXa from interacting with its substrates, thereby inhibiting clot formation. FXa (and thrombin) are common to both the intrinsic and extrinsic activation pathways in the coagulation cascade. Therefore, blocking FXa has the potential to provide more effective anticoagulation than would blocking other enzymes in the cascade.¹³ In general, direct FXa inhibitors, which are administered orally, have faster onsets of action and shorter half-lives than existing anticoagulants.¹⁴ Research has suggested that direct FXa inhibitors, in general, may be safer and more convenient than older anticoagulants because they are intended to be administered in fixed dosages, do not require monitoring, have few or minimal interactions with drugs or diet, and have a rapid onset of action that eliminates the need for parenteral anticoagulation.¹⁵

Although thrombin is also common to both the intrinsic and extrinsic activation pathways, it has been suggested that FXa may be a more logical target for anticoagulation, because it is located upstream of thrombin and is known to be a “primary site of amplification; one molecule of FXa catalyzes the formation of ≈ 1000 thrombin molecules.”¹³ At the same time, because FXa inhibition does not directly inhibit thrombin activity, some thrombin traces may “escape neutralization,

thereby facilitating hemostasis and leading to a favorable safety profile with respect to bleeding.”¹⁶ Additionally, FXa activates clotting over a broader concentration range than does thrombin, signifying that drugs that inhibit FXa’s actions would have wider therapeutic window.¹³

Apixaban (Eliquis[®], Bristol-Myers Squibb, New York, NY, and Pfizer, Inc., New York, NY) is an orally administered, highly selective, direct FXa inhibitor that is being investigated for preventing stroke in patients with AF, as well as for treating and preventing VTE.¹⁷ Because apixaban does not induce or inhibit cytochrome P450 (CYP) enzymes, the agent might have a low risk of drug-drug interactions relative to currently used anticoagulants, researchers suggest.⁴ Additionally, apixaban is “partly eliminated by the kidneys (25%) and, to some extent, also processed via CYP-independent mechanisms in the liver,” which may have implications for treating patients with mild to moderate hepatic or renal impairment.⁴ Apixaban has a terminal half-life of 10–14 hours and in clinical trials is being dosed twice daily.^{4,18-20}

Edoxaban (Lixiana[®], Daiichi Sankyo Co., Ltd., Tokyo, Japan) is a direct, oral, once-daily FXa inhibitor that is being investigated in the United States for preventing stroke in patients with AF and for treating VTE.^{21,22} According to its manufacturer, edoxaban is highly specific for FXa, which suggests that it would have little effect on the enzymatic activities of other serine proteases.^{11,23} The manufacturer also states that the drug has a predictable pharmacokinetic and pharmacodynamic profile, which allows it to be dosed once daily.²³

Rivaroxaban (Xarelto[®], Janssen Pharmaceuticals unit of Johnson & Johnson, New Brunswick, NJ, and Bayer AG, Leverkusen, Germany) is a direct FXa inhibitor that was recently approved in the United States for reducing the risk of blood clots, deep vein thrombosis, and pulmonary embolism following knee or hip replacement surgery and for reducing the risk of stroke in patients with AF.^{24,25} According to researchers who have investigated the drug in clinical trials, rivaroxaban exhibits predictable, dose-proportional pharmacokinetics and its pharmacodynamics are closely correlated with its plasma concentration. The agent has a dual mode of elimination through both the kidneys and the liver.²⁶ The researchers state that rivaroxaban is unlikely to interact with other drugs (e.g., digoxin, aspirin, nonsteroidal anti-inflammatory drugs) and has not yet been shown to interact with food, suggesting that dietary restrictions are unnecessary in patients receiving the agent.²⁶ Based on these attributes, the researchers state that monitoring clotting parameters is not necessary with rivaroxaban.²⁶ Rivaroxaban is administered orally, once daily.²⁷

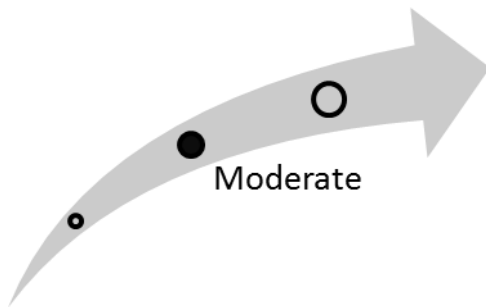
While manufacturers of FXa drugs in development have not yet released information regarding the potential per-patient cost of the drug for the intended indications in the United States, it is likely that they will be positioned at a price point similar to those of other novel oral anticoagulants that have entered the market (e.g., dabigatran, rivaroxaban) or may enter it (e.g., apixaban, edoxaban, betrixaban). The reported average wholesale price (AWP) of the FXa inhibitor rivaroxaban is \$8.10 per 10 mg tablet, which is a typical daily dosage after knee or hip surgery, although dosage can also be 20 mg/day depending on the patient and clinical circumstance. Thus, the AWP for a month supply of 30 tablets (10 mg) would be \$243.

Clinical Pathway at Point of This Intervention

According to practice guidelines from the American College of Cardiology/American Heart Association (ACC/AHA), preventing thromboembolism is an important component of AF management and is recommended for all patients with AF, except those with lone AF (i.e., AF that does not involve underlying heart abnormality or disease) or contraindications to the therapy.²⁸ Generally, ongoing treatment with a vitamin K antagonist (e.g., warfarin) is recommended, although aspirin may be substituted if warranted (e.g., the patient is considered low risk for thromboembolism or has contraindications to vitamin K antagonists).²⁸ A recent update to the guidelines incorporated the option of treating patients with dabigatran, stating that the drug may be

“useful as an alternative to warfarin” in certain patients.²⁹ For preventing and treating VTE, clinicians may administer unfractionated heparin, LMWH, fondaparinux, or warfarin; the specific agent used depends on several factors, such as whether the patient is undergoing orthopedic surgery, whether the patient is being treated on an inpatient or outpatient basis, and physician preference.^{1,30,31}

Figure 1. Overall High Impact Potential: Novel pharmacotherapies for anticoagulation



Experts commenting think these agents would not require the same ongoing laboratory monitoring that warfarin does, and would reduce health care infrastructure and testing needs (e.g., “Coumadin clinics”), staffing needs, and costs associated with monitoring if the agents diffuse. Experts also suggested that because the agents are orally available, they may provide a benefit over available parenteral anticoagulants. Because the drugs are orally self-administered by the patient, they can easily be adopted into current care models, according to these experts. Based on this input, our overall assessment is that this intervention is in the moderate end of the high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered comments on dabigatran.³²⁻³⁷ Seven experts, with similar backgrounds, offered comments on apixaban.³⁸⁻⁴⁴ Seven experts, with similar backgrounds, offered comments on edoxaban.⁴⁵⁻⁵¹ Seven experts, also with similar backgrounds, provided comments on rivaroxaban.⁵²⁻⁵⁸ One of the experts commenting on apixaban disclosed a potential conflict of interest, because the expert’s spouse works for Pfizer, the codeveloper of the drug.⁴¹ One of the experts commenting on edoxaban disclosed a potential conflict of interest, because the expert performs research and consulting duties with the manufacturers of several anticoagulants.⁵¹ These experts’ perspectives were balanced by the perspectives of experts who did not report conflicts of interests.

Despite the availability of other anticoagulation agents, the limitations associated with these drugs represent an important unmet need, experts agreed. In particular, experts highlighted the current agents’ unpredictable anticoagulation response, routine monitoring requirements, food and drug interactions, or injectable means of administration. Experts appeared to be confident that the newer agents have the potential to address these limitations. Their confidence was based on the well-understood mechanism of action through which these drugs exert their effects and on data from clinical trials that have been performed and reported on for these agents. However, experts also noted that as more of these drugs are approved and reach market, the unmet need becomes less important.

Experts appeared to agree that the greatest impact these agents will have on the health care system will be the reduced need for ongoing patient monitoring. Because these agents do not require the same ongoing laboratory monitoring that warfarin does, health care infrastructure and testing needs (e.g., “Coumadin clinics”), staffing needs, and costs associated with monitoring would

all be reduced if the agents become diffused, experts believe. Experts also suggested that because the agents are orally available, they may provide a benefit over available parenteral anticoagulants.

Experts thought that clinicians and patients will likely readily adopt these agents. As one clinical expert summarized, “Clinicians will most likely find the intervention to be a very attractive treatment option compared to ...available...medications used...due to its ease of use (oral administration, lack of need for routine laboratory testing to monitor anticoagulation, lack of need for dietary restrictions, and few drug interactions) and comparable efficacy.”³⁴

Many experts commented that these novel agents are more expensive than older generations of anticoagulants. However, some experts thought that the cost of taking one of these agents would be offset by a reduced need for ongoing monitoring and physician visits (e.g., for dose adjustments) and their associated costs. Some experts suggested that with the introduction of several new agents to the anticoagulation market, costs might be lowered to remain competitive within the market.

Arrhythmia Interventions

Cardiac Pacing System (Revo) for Patients Who May Require Future Magnetic Resonance Imaging

As the use of cardiac pacemakers has grown, so has the use of magnetic resonance imaging (MRI) for various clinical indications. However, the strong magnetic fields produced by MRI are known to pose potential risks to patients with implanted cardiac pacemakers, which contain metal components. MRI scanner effects on implanted cardiac devices can include heating of the electrode tips, migration or movement of the device, malfunction or damage of the device, and changes in pacing thresholds.⁵⁹ MRI technologists have attempted to modify imaging sequences to avoid complications in patients with implanted pacemakers, but many clinicians as well as patients are unwilling to risk MRI. To address concerns about pacemaker-compatible MRI imaging, one company has developed a new pacemaker, which recently received marketing approval. The Revo MRI[™] SureScan[®] pacing system (Medtronic, Inc., Minneapolis, MN) is a dual-lead, electronic, implantable cardiac pacemaker engineered to allow patients to safely undergo MRI scans under specific conditions. The complete system includes the Revo MRI SureScan IPG (implantable pulse generator) and two CapSureFix[®] MRI SureScan leads for use in an MRI environment. FDA approved Medtronic's premarket approval application in February 2011. The pacemaker is approved as "MR-conditional," meaning it can be used in an MRI environment under certain conditions according to the type of MRI scanner and scanner settings.⁶⁰⁻⁶²

Wilkoff and colleagues (2011) reported the results from a phase III, controlled trial of 464 bradycardia patients with a Revo pacemaker; 258 patients underwent MRI, and 206 control patients had no MRI. No MRI-related complications—which include sustained ventricular arrhythmias, pacemaker inhibition or output failures, electrical resets, or other pacemaker malfunctions—occurred during or after MRI procedures. Pacing capture threshold and sensed electrogram amplitude changes were minimal and similar between study groups.⁶³

The list price for the Revo is \$13,000, according to Medtronic. Hospitals and group purchasing organizations typically negotiate significant discounts on such devices. The U.S. Centers for Medicare & Medicaid Services (CMS) had ruled that it would provide Medicare coverage for MRI scans only in patients with MRI-compatible pacemakers in the context of a registered clinical trial. However, after the Revo device received FDA marketing approval, CMS revised its position to provide Medicare coverage for MRI scans in patients who have received an FDA-approved MRI-compatible pacemaker under certain conditions. In its July 2011 Final Decision Memorandum on Magnetic Resonance Imaging, CMS determined that adequate evidence was available to conclude the following:⁶⁴

“(MRI) improves health outcomes for Medicare beneficiaries with implanted permanent pacemakers (PMs) when the PMs are used according to the FDA-approved labeling for use in an MRI environment” and stated that it would “remove the contraindication for Medicare coverage of MRI in beneficiaries with implanted PMs when the PMs are used according to the FDA-approved labeling for use in an MRI environment. Other contraindications that may be present in any given beneficiary would continue to apply in patients with PMs.”

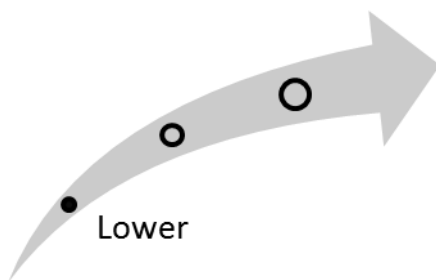
Clinical Pathway at Point of This Intervention

Cardiologists recommend implantation of an electronic cardiac pacemaker for a number of conditions that create various heart rhythm abnormalities. Clinical guidelines recommend implantation of cardiac pacemakers for several indications (with various subcategories within each broad indication), including acquired atrioventricular block in adults, atrioventricular block

associated with acute myocardial infarction, chronic bifascicular block, hypersensitive carotid sinus syndrome, hypertrophic cardiomyopathy, neurocardiogenic syncope, and sinus node dysfunction. Permanent pacemaker implantation is recommended in children, adolescents, and adults with certain congenital heart defects. Certain patients who undergo heart transplantation might require permanent pacemaker implantation to treat bradycardia (slow heartbeat). Patients with certain neuromuscular disorders, such as myotonic dystrophy and Emery-Dreifuss muscular dystrophy, might require pacemaker implantation.⁶⁵

The strong magnetic fields produced by MRI pose a risk to patients with implanted cardiac pacemakers, which contain metal components. These MRI-related device problems can cause arrhythmia or death. Thus, current clinical guidelines discourage the use of cardiovascular MRI in patients with implanted pacemakers. The exception would be when cardiovascular MRI is performed at highly experienced centers in cases with a strong clinical indication and when the potential benefits of cardiovascular MRI significantly outweigh the potential risks of the procedure.⁶⁶ The dual-lead Revo MRI SureScan pacing system would be used in place of conventional, non-MRI-safe, dual-chamber, cardiac pacemakers for the same types of clinical indications.

Figure 2. Overall High Impact Potential: Cardiac pacing system (Revo) for patients who may require future magnetic resonance imaging



Experts commenting on this new device were divided about its potential impact. On one hand, experts agreed that having the capability to conduct MRI scans in patients with pacemakers is important. However, novel protocols are being investigated to determine whether or not conventional pacemakers can be used in this capacity, which could obviate the need for the Revo. Although experts thought acceptance of the device would be high for both clinicians and patients, costs, training requirements, and lack of data might temper its diffusion. Based on this input, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, commented on this intervention.⁶⁷⁻⁷³

According to experts, the primary advance this device offers is expanding the patient population (to include those who have a pacemaker) that will be eligible for MRIs. Experts purport that this unmet need is important, given the valuable diagnostic information that MRIs provide and the numbers of patients with pacemakers. As one clinical radiologist pointed out, “In radiology, CT cannot substitute for MRI in some cases. For example, the soft tissue contrast in the peripheral joints is much greater with MRI than CT, and as such patients with a pacemaker who need an MRI would greatly benefit from this intervention.”⁶⁷ Another expert, with a background in cardiology, stated that “Clearly, MRI has become a critical diagnostic test for a number of diseases in almost every organ system,” and that “the potential adverse events that might occur when MRI is applied to patient with cardiovascular implantable endovascular devices (CIED) has been seen as a major

disadvantage to the use of the [CIEDs].”⁶⁸ However, this same expert noted that some medical institutions (e.g., Johns Hopkins, Baltimore, MD) have conducted research that suggests that “MRI may be applied safely to most patients with a currently manufactured CIED with only a few precautions.”⁶⁸

Experts were less agreed on whether this intervention will improve patient health outcomes. While several experts noted that the ability to use MRI in these patients might improve treatment decisions and diagnostic practices, others noted that the device itself does not have a direct therapeutic benefit. Despite these observations, experts generally agreed that most clinicians and patients would readily accept the technology, provided that the training involved and the technology costs are manageable. However, a couple of experts pointed out potential barriers to clinical acceptance of this technology. For example, one expert noted that the Revo, while MRI-compatible, does not have all of the capabilities that other CIEDs on the market have, potentially prompting physicians to choose a different pacemaker. Several experts noted that clinicians would likely prefer to have longer-term data on the pacing efficacy and safety of the Revo device. More than one expert noted that this device would require new MRI scanning protocols, and that the care team would need to be extensively trained on these.

Experts thought that this technology would have measurable impact on health care costs. First, several experts noted that the cost of the Revo was higher than costs of other pacemakers. Second, experts thought that costs will also rise as the number of MRI scans performed increases.

Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD) for Prevention of Sudden Cardiac Arrest

While implantable cardioverter-defibrillators (ICDs) are established therapy for preventing sudden cardiac arrest (SCA), their transvenous electrode leads have been associated with lead failure that can generate unnecessary shocks or fail to provide necessary shocks. When faulty leads are removed and replaced, substantial morbidity and mortality can occur. Lead problems occur in an estimated 40% of cases and have prompted development of a leads-free ICD system.⁷⁴

The S-ICD[®] System (Cameron Health, Inc., San Clemente, CA) is a subcutaneously implanted defibrillator that is being investigated for preventing SCA. According to its manufacturer, the S-ICD is intended to be minimally invasive and does not require electrode leads to be placed in or on the heart. Furthermore, the device does not require imaging equipment for placement because the system components are designed to be positioned using only anatomic landmarks.⁷⁵

The manufacturer describes the system components as a pulse generator, an electrode, and a programmer.⁷⁶ The battery-powered, computer-controlled pulse generator is intended to detect cardiac activity and provide defibrillation therapy. The subcutaneous electrode is partially coated and is designed to be implanted above and to the left of the sternum. The external programmer is designed to allow clinicians to set parameters for the pulse generator and to retrieve data.⁷⁷

According to the manufacturer, the implant procedure for the S-ICD is as follows. A surgeon makes an incision on the left side of the chest, next to the rib cage, and a pouch is formed under the skin for the placement of the pulse generator. The surgeon makes two small incisions to the left of the sternum allowing placement of the subcutaneous electrode under the skin. The subcutaneous electrode is connected to the pulse generator, tested, and adjusted using the external programmer, and the incisions are closed.⁷⁸ Because the system is entirely subcutaneous and can be placed using only anatomic landmarks, imaging equipment is not required during the procedure. The manufacturer claims the procedure should not usually require an overnight stay.⁷⁹

The S-ICD system is being investigated in clinical trials in the United States. The company submitted a premarket approval application for the device to FDA in January 2012.⁸⁰ FDA granted the device expedited review, and if the device is approved in 2012, the company anticipates product launch in the United States possibly by the end of 2013.^{81,82} The device received Conformité Européenne (CE) mark in 2009 for distribution in Europe.⁸³

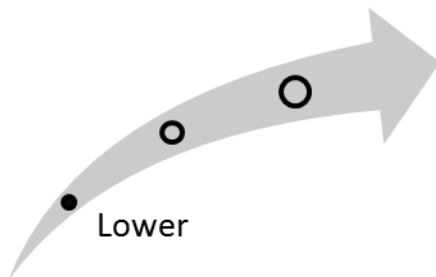
In a clinical trial of 64 patients in whom either the S-ICD system or single- (SC-TV) and dual-chamber (DC-TV) transvenous ICD system were implanted, authors concluded, “Appropriate detection of ventricular tachyarrhythmias for subcutaneous and TV devices in single- and dual-zone configurations was 100% and >99%, respectively. Specificity for supraventricular arrhythmias was significantly better for the S-ICD system compared to 2 of 3 TV systems, as well as the composite of TV devices (98.0% [S-ICD] vs 76.7% [SC-TV range: 64.0-92.0%] vs 68.0% [DC-TV range: 32.7-89.8%; $P < 0.001$]).”⁸⁴

Clinical Pathway at Point of This Intervention

According to the American College of Cardiology (ACC) and AHA, prophylactic ICDs are the preferred treatment for patients with ventricular fibrillation who are at risk for SCA. For patients who do not meet criteria for an ICD, beta blockers are considered first-line therapy, and radiofrequency ablation might be indicated. For patients with ventricular fibrillation refractory to ICD, drug therapy and radiofrequency catheter ablation or antiarrhythmic surgery might be warranted.⁸⁵

If approved for marketing, the S-ICD system would compete directly with other nonsubcutaneous ICD systems. If the S-ICD system is shown to be safe and effective, clinicians might prefer it to other ICD systems because it offers the potential to reduce lead-related adverse events and does not require imaging during placement.

Figure 3. Overall High Impact Potential: Subcutaneous implantable cardioverter-defibrillator (S-ICD) for prevention of sudden cardiac arrest



Overall, experts commenting on this topic expressed that this intervention might have some potential to improve patient health outcomes by reducing complications associated with lead-based ICDs and associated secondary surgeries that carry a high risk of morbidity and some mortality. Because the implantation procedure requires fewer resources and can be performed in an outpatient setting, this intervention could shift care delivery to a less invasive setting and shorter hospital stays. However, some experts suggested that this device's limited capabilities, compared with other ICDs, might temper its diffusion. Based on this input, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, commented on this intervention.⁸⁶⁻⁹¹ One of these experts declared a potential conflict of interest because the expert is a electrophysiologist who acts as a consultant to Cameron Health and as an investigator for the S-ICD investigational device exemption study.⁸⁸ This potential conflict of interest is balanced by the perspectives of other experts who did not declare conflicts of interest.

Experts generally agreed that the unmet need this intervention is purporting to address is important, based on both the “high incidence of lead failure in conventional ICDs and the high morbidity and mortality associated with lead failure and replacement in these devices.”⁸⁶ Most experts thought that this intervention has the potential to meet this need, although a few experts suggested that longer-term data will be necessary before clinicians will fully adopt the technology and that this device's diffusion might be limited by its limited pacing capabilities. One expert, speaking from a clinical perspective, stated: “The main advantage of the system is its degree of invasiveness, which is much less [than currently available ICDs]. However, there are substantial weaknesses with a device that does not have a lead, ... does not advocate [its] ability to [conduct] event tachycardia pacing or bradycardia pacing, ... with a device that is large and placed in the axilla.”⁹⁰

Experts were generally of the opinion that S-ICD would exert an effect on patient outcomes, partly because of the theory underlying the technology, but also because of the data collected thus far.

Because ICD placements are common, this intervention is unlikely to significantly disrupt current care models or operations processes, with a few exceptions, the experts noted. First, because the device is leadless and can be placed using only anatomic landmarks, it might allow for placement of devices in an expanded number of venues. For the same reasons, there might be less

need for specialized procedure rooms and fluoroscopy/imaging, the experts commented. They also noted that surgeons implanting the device might require some initial S-ICD-specific training. Experts commenting also noted that the device can be implanted in an outpatient setting, which would shift care from the inpatient to outpatient setting that is associated with available ICDs.

Although the S-ICD cost is similar to that of other ICD systems, experts thought that this intervention has the potential to reduce some financial burden by avoiding lead complications and shifting the setting from inpatient to outpatient surgery. Experts agreed that both patients and clinicians would likely adopt this device if it is effective relative to existing ICDs, although several experts commented on the need for longer-term data if this is to occur.

Heart Failure Interventions

Autologous Mesenchymal Stem Cell Transplantation (C-Cure) for Treatment of Heart Failure

First-line treatments for heart failure (HF) are typically palliative and address only disease symptomology, rather than the underlying loss of cardiomyocytes that is the hallmark of the disease.⁹² In light of this, stem cells have been investigated as a means of improving the heart's capacity for self-repair.⁹² First-generation, "undifferentiated" stem-cell therapies for HF have shown limited clinical benefit in early clinical trials. Therefore, researchers are now suggesting pretreating cells with "activators" designed to improve the cells' cardiac homing ability and possible survival in cardiac tissue.⁹³

C-Cure[®] (Cardio3 Biosciences, S.A., Mont-Saint-Guibert, Belgium) is a bone-marrow-derived, cardiopoietic, mesenchymal stem cell therapy that is being investigated for treating heart failure.⁹⁴ The therapy involves harvesting mesenchymal cells from the patient's bone marrow, treating the cells with growth factors (a "cardiopoietic cocktail"), and then injecting the cells into the patient's heart.⁹⁴ The cocktail includes transforming growth factor-beta1, bone morphogenetic protein-4, activin A, retinoic acid, insulin-like growth factor-1, fibroblast growth factor-2, alpha-thrombin, and interleukin-6.⁹⁵ The company claims that treatment with these proteins can transform mesenchymal (undifferentiated) stem cells into cardiac progenitor cells to replicate natural cardiogenesis, without modifying the genome of the cell.^{94,96} The cardiac progenitor cells are designed to behave identically to cells lost during progression of heart failure, and they potentially regenerate damaged heart muscle without risk of rejection.⁹⁷

In clinical trials, the stem cells have been initially collected from the patient's iliac crest. After cells are treated ex vivo, they are administered into the patient's left ventricle via 20 endomyocardial injections at sites bordering the damaged heart tissue. According to the company, this process takes place during a single surgical procedure, and cardiac electromechanical mapping is used to identify injection sites.^{95,96}

According to an April 2011 company press release, researchers reporting on a phase II trial of 45 patients with severe HF of ischemic origin in Belgium and Serbia who were treated with optimal standard of care or optimal standard of care plus C-Cure concluded, "Patients receiving C-Cure saw an 18.1% increase in left ventricular ejection fraction (LVEF), a measure of heart function, over baseline, as measured by echocardiography, while the mean LVEF improved only marginally in patients enrolled in the control group. This difference in LVEF between the C-Cure treated and control patients was significant ($p < 0.01$) suggesting that C-Cure treatment leads to heart tissue repair."⁹⁸ In September 2011, the company reported that it planned to discuss the phase II results with FDA and the European Medicines Agency before finalizing the protocol for the phase III trials.⁹⁹ The company planned to begin a large, phase III trial at European and U.S. centers by the end of 2011 to support applications for marketing in Europe and the United States, but as of February 2012, the trial had not been registered on the National Clinical Trials database.^{95,100} In September 2011, Cardio3 announced that it had established a subsidiary in Rochester, MN, to support the expansion of the company's clinical and regulatory activities in the United States.⁹⁹

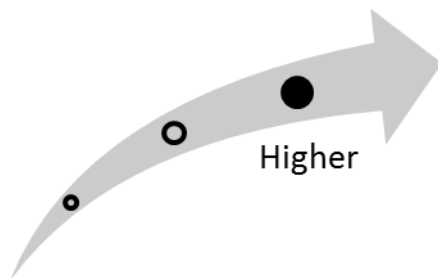
Clinical Pathway at Point of This Intervention

In general, first-line medical HF management includes angiotensin-converting enzyme inhibitors and beta blockers, with the option of adding angiotensin receptor blockers, digoxin, diuretics, or aldosterone antagonists to the treatment regimen for certain subpopulations.^{101,102} In some cases, surgical intervention (e.g., coronary bypass surgery, heart valve repair or replacement, ventricular-assist device implantation) may be indicated. Patients with severe HF may require a

heart transplant.¹⁰² If approved by FDA for marketing in the United States, C-Cure stem cell therapy would likely be positioned as the first regenerative therapy available for patients with HF.

This stem cell therapy may reduce the need for pharmacotherapies that address symptoms of HF. However, it should be noted that in clinical trials investigating the use of guided stem cell therapy, patients receiving the intervention remained on a regimen of standard-of-care medical therapy. Thus, the company may intend for the stem cell therapy to be used in conjunction with standard medical therapy. If approved for marketing, the stem cell therapy also has the potential to displace some of the need for other surgical interventions used as HF advances. The lifestyle changes (e.g., diet, exercise) that often accompany HF treatment would likely remain complementary interventions to stem cell therapy.

Figure 4. Overall High Impact Potential: Autologous mesenchymal stem cell transplantation (C-Cure) for treatment of heart failure



Although some experts remain skeptical about this intervention's potential efficacy until larger or long-term trials are completed, experts generally agreed that this intervention may have dramatic effects on the health care system, should its efficacy be proven. Furthermore, experts consider the need for disease-modifying HF therapies to be extremely important. As a potentially disease-modifying therapy for HF, experts commented, this therapy has the potential to significantly affect certain parameters of the health care system, including increasing the initial cost associated with treating HF and establishing a treatment paradigm that treats the disease instead of the disease's symptoms. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, health administration, and health systems backgrounds, provided perspectives on this topic.¹⁰³⁻¹⁰⁸

Experts strongly agreed that the need for disease-modifying treatments for HF is exceptionally important, given the high and increased prevalence of the disease, the inability of current treatments to reverse or slow its progression, and its associated mortality and decreased quality of life for patients. In general, experts were optimistic about this intervention's potential to meet this need, based on both available trial data and the scientific theory underlying the intervention. One research-based expert, with expertise in the field of regenerative medicine, stated: "C-Cure has a great potential to improve patient health as the preliminary results from clinical trials were very promising, not only showing great safety but also significant improvements in heart function. These results are supported by numerous studies of mesenchymal stem cells improving cardiac function and recovery after infarct or other heart damage."¹⁰⁸ However, more than one expert noted that longer-term, larger trials are needed before any definitive predictions can be made about the intervention's efficacy. An expert with a background in cardiology stated, "Many promises with stem cell therapy so far have not been fulfilled."¹⁰⁵

Experts generally asserted that, if effective, this treatment has the potential to disrupt health care processes. First, the focus of care would shift to regeneration and the underlying cause of HF, rather than on treatment of symptoms. Second, experts indicated if this intervention were to be proven effective, it has the potential to obviate the need for expensive interventions (e.g., coronary bypass, heart transplantation) for patients with late-stage HF. Third, experts often commented that this treatment requires a surgical procedure during a stage of HF that has previously been treated only with pharmacotherapy. Some experts noted the infrastructure changes that this intervention would necessitate, such as expansion of facilities and care teams. However, some experts noted that despite these initial changes, the intervention might obviate the need for other, invasive procedures or pharmacotherapy, thereby reducing demand for care over time.

Experts agreed that this procedure would be likely to be very expensive initially, based on the costs of the stem cell harvesting and treatment and the surgical injection procedure, but that it could reduce costs over time, especially if HF progression is reversed and, in turn, the need for additional HF interventions is obviated. Some experts thought that these costs would be prohibitively high for patients, especially in the absence of insurance coverage. Although experts generally thought that most patients and clinicians would accept this procedure, given the lack of other disease-modifying treatments for HF, several experts suggested that the invasiveness of the procedures involved in this therapy would pose a barrier to acceptance for some patients.

Portable Freedom Driver for In-Home Support of the Total Artificial Heart

The temporary Total Artificial Heart (TAH-t, SynCardia Systems, Inc., Tucson, AZ), is a pneumatic, biventricular, implantable device that functions in place of the two ventricles and four valves of a failing heart by pumping blood to both the pulmonary and systemic circulations.¹⁰⁹ The TAH-t, approved as a bridge-to-transplant by FDA in October 2004,¹¹⁰ is indicated for use in cardiac-transplant-eligible patients at risk of imminent death from nonreversible biventricular failure.¹⁰⁹ The TAH-t is powered by a conventional pneumatic driver system, which is a large and cumbersome device that requires patients to remain hospitalized while awaiting a donor heart.¹¹¹ A portable driver system that could allow patients to be discharged from the hospital while awaiting a suitable donor heart might address a significant unmet need for this small patient population.

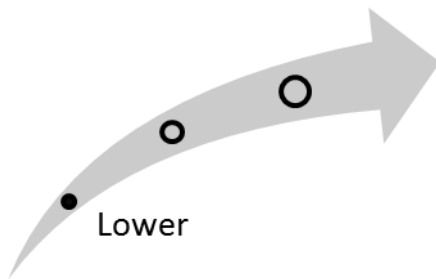
The Freedom[®] Driver System, also developed by SynCardia Systems, is under development to address this need. It is a wearable pneumatic driver that powers the SynCardia TAH-t. The driver is intended to allow patients receiving the TAH-t to leave the hospital and live at home while awaiting a donor heart. The 13.5-lb pneumatic driver is carried in a backpack or shoulder bag. The driver is powered by two onboard batteries that can be recharged with an automobile adapter or a standard electrical outlet. As with conventional, large, hospital-based pneumatic driver systems, the Freedom driver is connected to the implantable TAH-t by a flexible pneumatic driveline that passes through the patient's skin in the left chest just below the ribs. The driver flashes a light or sounds an alarm when the system requires the user's attention.¹¹¹

In March 2010, SynCardia received Conformité Européenne (CE) mark approval to market the Freedom driver in the European Union for use with the SynCardia TAH-t.¹¹² The portable driver is being studied under an FDA-approved investigational device exemption (IDE).¹¹³ As of January 2012, the company had reported that 35 patients implanted with the TAH-t had been enrolled and that 23 of these patients had been discharged from the hospital using the portable driver.¹¹³ Although literature results have not identified any completed clinical trials using the driver, the clinical experience of one patient has been published.¹¹⁴ According to a July 2011 press release, a 41-year-old male, who received the TAH-t as a bridge to transplant, was discharged from the hospital using the portable driver system, which supported him for a total of 253 days, at which point he returned to the hospital to receive a dual heart and kidney transplant.¹¹⁴

Clinical Pathway at Point of This Intervention

The American College of Cardiology/American Heart Association clinical guidelines identify cardiac transplantation or the implantation of a ventricular assist device (VAD) as the only established surgical treatments for advanced, end-stage HF.¹¹⁵ The portable driver system is intended to complement TAH-t use.¹⁰⁹ As a bridge to transplantation, the TAH-t with the Freedom driver would complement heart transplantation. Some left VADs that are compatible with portable driver systems for in-home use could compete with the TAH-t and Freedom driver as a bridge to transplantation.

Figure 5. Overall High Impact Potential: Portable driver system (Freedom Driver) for total artificial heart



Although the patient population for which this device is intended is small, and in-hospital driver systems already exist, a portable driver for the TAH-t system has the ability to dramatically improve patient quality of life and dramatically shift the care setting by allowing patients to return home while awaiting transplant, experts commenting on this intervention agreed. Experts also thought that this device has the potential to reduce costs associated with lengthy hospital stays and that using the portable device would require additional resources, such as training for staff and family members. Based on this input, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.¹¹⁶⁻¹²²

While the patient population for which this device is intended is small, experts generally agreed that an important unmet need exists for a driver system that would allow these patients to be discharged home while awaiting a heart transplant. Rather than closing a true gap in unmet need for health technology (because inpatient drivers are already available in the hospital setting), this device's greatest benefit is improving patient quality of life and affecting costs of care by shifting from inpatient to at-home care while awaiting a heart transplant.

In general, experts were confident that this device would improve patient quality of life, due to the psychological benefit of being able to remain home with family members while awaiting a heart transplant, and due to the potential health benefit that would arise from increased mobility. Some experts likened this the potential of this technology to that of ventilators and ventricular assist devices, which were previously only offered in the hospital setting, but have since been moved to the home care realm with positive results. Experts also suggested that there may be a health benefit in removing patients from the hospital setting, given the high risk for nosocomial infections associated with inpatient care.

Experts noted that shifting the patient's care setting from an inpatient setting to the home is important, and would likely result in a marked decrease in costs, given the expense of continual, long-term inpatient care. For this reason, and for the potential improvements in quality of life and health status for patients, experts thought that both clinicians and patients would readily adopt this technology, provided long-term data are positive. Several experts also noted that extensive training (on the part of both hospital staff and patient home caregivers) would be required for diffusion of this product, but did not expect this to be a barrier to uptake. Additionally, experts thought that this shift would "substantially impact the aftercare community and require additional collaboration and coordination between inpatient and outpatient facilities."¹¹⁹

Hypertension Intervention

Radiofrequency Ablation Renal Denervation (Symplcity System) for Treatment-Resistant Hypertension

Many pharmacotherapies are available for treating hypertension, but still, uncontrolled hypertension persists in many patients.¹²³ Because uncontrolled hypertension is associated with high morbidity (e.g., end-stage organ damage) and mortality, novel interventions for treating this condition are needed.¹²³ The renal denervation device described in this report might offer a therapeutic intervention for patients whose hypertension remains uncontrolled, despite pharmacotherapy. This device also has the potential to shift hypertension care from the realm of pharmacotherapy alone to the realm of minimally invasive, permanent procedures.

The sympathetic nervous system is known to contribute to increases in blood pressure. In many patients with essential hypertension, efferent sympathetic outflow from the central nervous system to the kidneys is overactive. This activity modulates levels of renin release, tubular sodium reabsorption, and renal blood flow in ways that perpetuate hypertension.¹²⁴ Afferent renal sensory nerves, which carry signals from the kidneys to the central nervous system, also play a role in promoting sympathetic outflow, and are considered additional contributors to hypertension.¹²⁴ Surgical disruption of renal sympathetic nerves has been explored for decades as a potentially therapeutic intervention for hypertension. However, earlier approaches usually involved radical sympathetic denervation, which reduced blood pressure but was not targeted enough to avoid perioperative and long-term complications (e.g., bowel, bladder, erectile dysfunction; postural hypotension).¹²⁵

In an effort to mimic the blood pressure improvements seen with radical sympathetic denervation but avoid its associated side effects, manufacturers have begun investigating minimally invasive, catheter-based approaches to renal denervation.¹²⁵ The Symplcity[®] Renal Denervation System[™] (Ardian, Inc., now part of Medtronic, Inc., Minneapolis, MN), one such system, uses radiofrequency energy delivered via catheter technology to selectively ablate afferent and efferent renal nerves located in the adventitia of the renal arteries.¹²⁴ The manufacturer purports that deactivating the renal nerves using this process will selectively reduce “both the pathologic central sympathetic drive to the kidney and the renal contribution to central sympathetic hyperactivity,” potentially resulting in a sustained reduction in blood pressure.¹²⁶ According to its manufacturer, the system comprises two components: a generator, which automatically controls the radiofrequency energy delivery and is controlled by a foot pedal; and a catheter, which applies the radiofrequency energy in the renal artery and is compatible with 6 Fr diameter guide catheters.¹²⁷⁻¹²⁹

The denervation procedure, which is conducted in a catheterization laboratory, is performed with the patient under conscious sedation and takes about 40 minutes.^{127,130,131} The manufacturer describes the procedures as follows: a surgeon introduces the catheter through the femoral artery, via a guide catheter, and threads it to the renal artery. The catheter’s tip is placed against the arterial wall, and clinicians deliver radiofrequency energy to the surrounding sympathetic nerves; the energy is controlled via a computer-controlled algorithm.¹²⁷ The surgeon may apply up to six ablations, lasting up to 2 minutes each, within each renal artery.¹³¹ The manufacturer states that because the one-time procedure does not involve a permanent implant, patients are able to recover and return to daily living quickly.¹²⁶

According to the manufacturer, this system is approved for marketing in the European Union and Australia.¹³² In July 2011, the company announced that it had received permission from FDA to begin the first randomized controlled trial in the United States to evaluate percutaneous renal denervation for treatment-resistant hypertension.¹³³ The Symplcity HTN-3 trial is scheduled to enroll about 530 patients at 60 U.S. sites. The primary endpoints will be change in baseline systolic

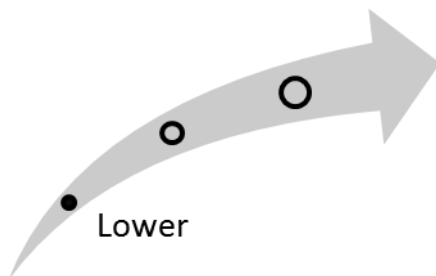
blood pressure at 6-month followup and incidence of major adverse events within 1 month after randomization.¹³³

In a clinical trial of the intervention in 153 patients at 19 centers in Australia, Europe, and the United States, published results state: "The median time from first to last radiofrequency energy ablation was 38 minutes. The procedure was without complication in 97% of patients (149 of 153). The 4 acute procedural complications included 3 groin pseudoaneurysms and 1 renal artery dissection, all managed without further sequelae. Postprocedure office BPs were reduced by 20/10, 24/11, 25/11, 23/11, 26/14, and 32/14 mm Hg at 1, 3, 6, 12, 18, and 24 months, respectively."¹³⁴

Clinical Pathway at Point of This Intervention

According to the most recent report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, lifestyle modifications (e.g., weight and diet management) are the initial interventions used in patients with hypertension.¹³⁵ If lifestyle changes do not result in satisfactorily controlled blood pressure, pharmacotherapy is indicated.¹³⁵ Medical management of hypertension includes thiazide-type diuretics, used alone or in combination with one of several classes of antihypertensive agents (e.g., angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, or calcium channel blockers).¹³⁵ If the Symplicity Renal Denervation System is approved for use in the United States, it is likely to be positioned for use in patients whose hypertension is not adequately controlled with three or more antihypertensive medications and is likely to be used in conjunction with these background therapies.^{127,136}

Figure 6. Overall High Impact Potential: Radiofrequency ablation renal denervation (Symplicity System) for treatment-resistant hypertension



Experts commenting on this intervention agreed that it has the potential to fill an important gap in treatment of hypertension and would likely be somewhat accepted by clinicians and patients. However, this intervention's potential impact is tempered by its lack of longer-term outcomes data, and the likelihood that it would be easily incorporated into existing health care infrastructure. Based on this input, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.¹³⁷⁻¹⁴³

Experts agreed that the need for interventions for treatment-resistant hypertension is important, due to the size of the affected population, the morbidity and mortality associated with the condition, and the dearth of available treatments, once pharmacotherapy fails to achieve desired outcomes. Although several experts noted that the data available for the intervention are limited, experts still were cautiously optimistic that this intervention is likely to improve patient health, citing the promising efficacy data that have been collected to date. However, several experts noted that longer-term studies are necessary to determine whether the reduction in blood pressure that has

been observed in trials translates to improved clinical outcomes, and to further clarify the safety profile of the intervention.

Most experts suggested that this intervention would not especially disrupt health care infrastructure, because the procedure will take place in a catheterization lab, which as one clinical expert stated, “could accommodate patient volume, assuming it is an outpatient procedure, is not associated with significant complication, and requires a single sitting application.”¹³⁷ However, several experts agreed that this intervention would be likely to increase the volume of patients seeking services from catheter facilities, and may represent a shift in patient management over the long term, should this intervention be proven to reduce the need for ongoing hypertension pharmacotherapy.

Experts were divided on whether this intervention would be readily accepted by both clinicians and patients. According to some experts, clinicians would be likely to adopt the technology because alternative treatments do not exist for this population and because the intervention requires only a one-time procedure. However, several experts expect that before adoption can occur, clinicians and patients will want to see more comprehensive safety and long-term efficacy data. Some experts suggested that the invasiveness of the procedure would pose a barrier to uptake. Most experts expected this intervention would have a moderate effect on health care costs. Although the initial procedure will be associated with an initial upfront cost, some of this initial outlay could be offset by the potential for future savings, if the intervention is proven to improve patient health.

Myocardial Infarction Intervention

Standardized Protocol and Integrated System (RACE Project) for Treatment and Transfer of Patients with ST-Elevation Myocardial Infarction

Despite the substantial amount of evidence that supports the effectiveness of rapid reperfusion therapy in patients with ST-segment elevation myocardial infarction (STEMI), an estimated 18% to 50% of patients eligible for therapy do not receive it.¹⁴⁴ Furthermore, fewer than half of patients in the United States receive reperfusion treatment within the timeframes recommended by current treatment guidelines.¹⁴⁴ Several systemic barriers might be responsible for these outcomes, and might include lack of integrated health care and coordination, competition issues, interfacility transfer transportation issues, administrative and/or legislative issues, and lack of standardized protocols and feedback. The Reperfusion of Acute Myocardial Infarction in North Carolina Emergency Departments (RACE) project is intended to integrate care between hospitals with and without primary percutaneous coronary intervention (PCI) capability to minimize time to reperfusion, thereby potentially improving outcomes in patients experiencing a STEMI.¹⁴⁵

The RACE quality improvement project was developed in North Carolina to address the aforementioned barriers by aligning physicians, nurses, hospitals, emergency medical service (EMS) personnel, professional societies, payers, and government in a regionally organized, collaborative, statewide initiative.^{144,145} The program goals are to overcome systematic barriers, decrease delays in administering reperfusion therapy, increase the frequency with which reperfusion is provided to eligible patients, and improve processes of care (e.g., improving the proportion of patients presenting via EMS who have prehospital 12-lead electrocardiograms [ECGs]).^{144,145} The program developers state that this program is intended to “establish a statewide system for reperfusion, as exists for trauma care, to overcome systemic barriers.”¹⁴⁶

For each hospital participating in the project, the RACE team (described in detail below) works with appropriate administrators, nurses, physicians, and technicians to devise a unique “coronary reperfusion plan,” based on medical evidence, published guidelines, available resources, and regional and local practice patterns.¹⁴⁶ The team uses a RACE project intake tool to evaluate current practice at a hospital, then uses that information along with hospital-specific data to determine appropriate system changes at all sites.¹⁴⁴ In devising recommendations for each component of the plan, the RACE team holds local, regional, and statewide meetings and conferences calls with local leaders and reviews progress during the course of the project in weekly conference calls among the RACE leadership team members.¹⁴⁶ Both hospitals with primary PCI capability and those without primary PCI capability (referring hospitals) participate in the program.¹⁴⁶

Even though the resulting systemic changes vary from hospital to hospital, the RACE team provides an overall set of recommendations to each hospital in the form of an operations manual.¹⁴⁶ According to the program’s developers, recommended interventions focus on each component of the reperfusion process, including the EMS, the emergency department (ED), the catheterization laboratory, and interhospital transfer.¹⁴⁶

Specific recommendations may include the following (as described by program developers in a November 2006 article in the *American Heart Journal*):¹⁴⁴

For EMS-level interventions, program developers may suggest prehospital ECGs, a communication process for ECGs, or identification of ST-segment elevation; standard history, physical, and a reperfusion checklist to be completed before hospital arrival; statewide training program for ECG interpretation; preferential transport to primary PCI for certain patients.¹⁴⁴

For EDs that do not have the ability to perform primary PCI, the RACE program may recommend an algorithm for fibrinolytic therapy rather than transfer for primary PCI, based on

American College of Cardiology/American Heart Association (ACC/AHA) guidelines; accurate information on typical transport times to primary PCI centers in region; establishment of a single-call system for each PCI center for patients needing transfer for primary PCI or rescue PCI.¹⁴⁴

For improving interhospital transportation, RACE leaders may recommend an algorithm for preferred method of transportation for each PCI center; direct transportation to a catheterization laboratory; streamlined use of local EMS (including leaving all patients on stretcher during ED rapid evaluation) for transport distances up to 50 miles; standards for rapid assessment (10 minutes from landing to takeoff time) and transfer with helicopter transport; the use of no intravenous heparin or nitroglycerin to streamline the transfer process (i.e., heparin bolus and nitroglycerin paste).¹⁴⁴

To improve primary PCI center communication, recommendations may include a single telephone line for calls for STEMI reperfusion; a policy to accept patients regardless of bed availability and to engage the catheterization laboratory without interventional cardiology consultation; and recording of all calls to tertiary centers for review and quality improvement.¹⁴⁴

For primary PCI center catheterization laboratories, changes may include the following: a plan for “thirty minutes from contact to catheterization laboratory readiness, 24 hours a day, seven days a week,” and immediate feedback, including recording and reporting first door-to-balloon time to the referring ED.¹⁴⁴

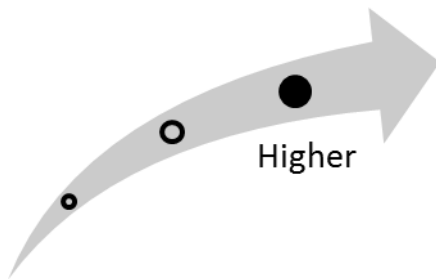
To date, the RACE model has been implemented in 68 hospitals in North Carolina, and is intended to be used as a model for reducing time-to-reperfusion in other statewide systems.¹⁴⁷ In a 2011 trial of 436 STEMI patients at 55 non-PCI hospitals, which looked at outcomes before and after implementation of the RACE model, the authors wrote:

Median door-in-door-out times improved significantly with the intervention (before: 97.0 minutes, interquartile range, 56.0 to 160.0 minutes; after: 58.0 minutes, interquartile range, 35.0 to 90.0 minutes; $P<0.0001$). Hospital, ED, and EMS care processes were each independently associated with shorter door-in-door-out times (-17.7 [95% confidence interval, -27.5 to -7.9]; -10.1 [95% confidence interval, -19.0 to -1.1], and -7.3 [95% confidence interval, -13.0 to -1.5] minutes for each additional hospital, ED, and EMS process, respectively). Combined, adoption of EMS processes was associated with the shortest median treatment times (44 versus 138 minutes for hospitals that adopted all EMS processes versus none).¹⁴⁵

Current Approach to Care

ACC and AHA recommend in their clinical guidelines that patients with STEMI should be treated with fibrinolysis within 30 minutes from symptom onset, or primary PCI within 90 minutes from onset.¹⁴⁴ However, various health care system factors present challenges in meeting these recommended treatment goals.¹⁴⁴ The RACE model was developed to address some of these factors and challenges on a systems level. In particular, the RACE model aims to reduce the time to primary PCI for patients transferred from hospitals that are not primary PCI-equipped to hospitals that are able to perform primary PCI.¹⁴⁶ Currently, only 4% of these patients are treated within the 90-minute treatment window.¹⁴⁴

Figure 7. Overall High Impact Potential: Standardized protocol and integrated system (RACE Project) for treatment and transfer of patients with ST-elevation myocardial infarction



Given the evidence base that supports timely PCI, and the large proportion of patients who are still not receiving it, experts agree that this intervention has the potential to address an important unmet need in the health care system. Besides disrupting current health care infrastructure and patient management models, experts thought, this intervention may also improve patient health outcomes and improve health disparities, particularly for rural populations. Although clinicians and patients are expected to accept this initiative, experts thought that issues of reimbursement and the potential for revenue losses at hospitals will need to be addressed before wide adoption will be possible. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this care delivery innovation.¹⁴⁸⁻¹⁵³ One expert was involved with the ACC's Door-to-Balloon project (of which the RACE participants were members) at the time of the RACE project, but the expert does not have input into the administration, development, or operation of the RACE initiative. This potential conflict of interest was balanced by the perspectives of experts who did not disclose conflicts of interest.

Experts strongly agreed that the unmet need this intervention purports to address is extremely important, given the number of patients affected and the life-saving nature of PCI when it is received within recommended time frames. Experts also agreed that this intervention has the potential to improve patient health outcomes. This opinion was based on both the promising data collected in trials to date, and the theory underlying the project, which lies in the accepted benefit of timely PCI care. As one health system's expert noted, "Numerous studies have confirmed the substantial benefits to patient outcomes that can be achieved by achieving door-to-balloon times of 60 minutes or less. The Race initiative demonstrates the new levels of performance, coordination, and communication that can be achieved within a region or state."¹⁵⁰

Experts also thought that this intervention may improve health disparities. One research-based expert stated "In theory, effective regional and statewide implementation of this type of program is likely to help ensure that the program is equally accessible, regardless of where the MI occurs or what hospital the patient is taken to."¹⁵² Specifically, experts thought that this program would be particularly effective in addressing health disparities that exist in rural areas.

Additionally, experts were confident that this intervention would have an impact on both hospital infrastructure and patient management models. As one clinical expert stated, "This proposal has the potential to disrupt current patterns of patient care at multiple levels (EMS, referring hospitals, academic centers)."¹⁴⁸ Furthermore, as one research-based expert stated, the project "requires major revision of EMS and ED services, involving planning and implementation, including training in an entirely new way of thinking about optimal care delivery in these settings."¹⁵²

Experts were optimistic that both clinicians and patients would welcome such a program. Experts thought that patients would appreciate the opportunity to receive more timely care, and that clinicians would be supportive of the program if it is shown to improve patient outcomes. Some experts, however, note that hospitals may be less accepting of this intervention until related reimbursement policies can be worked out. Several experts noted that this intervention will be somewhat costly to implement, and that some hospitals may lose revenue over time, due to the intervention. Experts think that this may pose a barrier to uptake, and suggest that this may be the reason some hospitals chose not to participate in this pilot project.

Valve and Structural Disorder Interventions

Off-Label Sildenafil (Viagra) for Improving Pediatric Exercise Tolerance After a Fontan Operation

The Fontan operation is a palliative surgical procedure that is primarily used in patients who have complex cardiac malformations that leave a single anatomical functional ventricle in the heart.¹⁵⁴ In these cases, the circulation must be surgically reconfigured to maximize the efficiency of the working ventricle without overburdening it.¹⁵⁵ Pediatric patients undergoing a Fontan procedure often experience compromised exercise capacity due to the inability of the reconstructed heart to keep up with the increased metabolic demand associated with exercise.¹⁵⁶ No medical therapies have demonstrated a benefit in improving exercise tolerance in patients who have undergone a Fontan operation, although exercise training may improve aerobic capacity in some patients.¹⁵⁷ Therefore, an unmet need exists for effective interventions that will improve patients' exercise capacity, which, in turn, can improve quality of life.

Sildenafil is a phosphodiesterase type 5 inhibitor that is FDA approved as treatment for erectile dysfunction (under the brand name Viagra®) and for pulmonary arterial hypertension (under the brand name Revatio®).¹⁵⁸ Sildenafil is known to exert a potent selective vasodilatory effect on the pulmonary vasculature, thereby lowering resistance in lung vessels and improving blood flow.^{156,159}

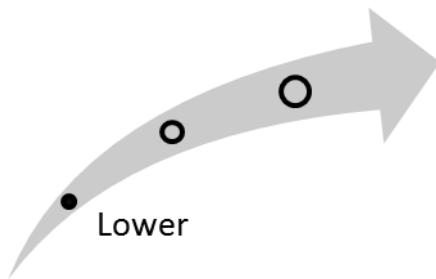
In patients with pulmonary arterial hypertension, a condition characterized by abnormally high lung resistance and a resulting inability of the heart to meet metabolic demands, sildenafil has been shown to improve exercise performance.¹⁵⁶ Because patients who have undergone a Fontan operation also manifest limited cardiac output due to lung resistance, academic and clinical researchers are now investigating the off-label use of sildenafil as a means for improving exercise capacity in these patients.¹⁵⁶ Researchers speculate that if the drug is effective, treated patients will have an improved efficiency of blood flow through the lungs and, as a result, improved cardiac output. These changes may offer patients the benefit of diminished symptoms; increased energy; an increased ability to walk, run, or play sports; and an improved quality of life.¹⁵⁶

In the most recent clinical trial investigating the off-label use of sildenafil in this population, 28 children and young adults with Fontan circulation were randomly assigned to receive placebo or sildenafil (20 mg three times daily) for 6 weeks, then, after a 6-week washout, crossed over for an additional 6 weeks. The author of this study stated: "After taking sildenafil, subjects had a significantly decreased respiratory rate and decreased minute ventilation at peak exercise. At the anaerobic threshold, subjects had significantly decreased ventilatory equivalents of carbon dioxide. There was no change in oxygen consumption during peak exercise, although there was a suggestion of improved oxygen consumption at the anaerobic threshold. Improvement at the anaerobic threshold was limited to the subgroup with single left or mixed ventricular morphology and to the subgroup with baseline serum brain natriuretic peptide levels ≥ 100 pg/mL."^{156,159}

Clinical Pathway at Point of This Intervention

No professional guidelines are available for managing pediatric patients who have undergone Fontan surgery, partly because of the paucity of data available to support the use of various interventions.¹⁵⁴ Because arrhythmias can occur after a Fontan procedure and can lead to abnormalities in clotting and platelet reactivity, some clinicians prescribe low-dose aspirin or warfarin; however, these therapeutic regimens have not been standardized.¹⁵⁷ If proven effective, sildenafil would likely be positioned as the first evidence-based pharmaceutical option for improving exercise capacity in patients who have undergone the surgery.

Figure 8. Overall High Impact Potential: Off-label sildenafil (Viagra) for improving pediatric exercise tolerance post-Fontan operation



Experts unanimously agreed that the unmet need this intervention purports to address is very important, given the quality of life and health-related effects of Fontan circulation. Experts also agreed that this intervention is likely to meet this need, in light of sildenafil’s mechanism of action and its easy administration. Experts thought the high cost of the off-label drug might slow its use. Our overall assessment is that this intervention is in the lower end of high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, and health system backgrounds, offered perspectives on this intervention.¹⁶⁰⁻¹⁶⁵ Experts agreed that although the population affected by this condition is small, the unmet need for improved exercise tolerance in patients with Fontan circulation is important, particularly in light of the importance of exercise to this population over the long term. One clinical expert noted that, “Although phrased by the researchers [investigating this intervention] in typical medical terminology as exercise tolerance, it is really activity tolerance. These patients have compromised ability to tolerate normal daily activities. Improvement of that status has significant quality-of-life potential in addition to the aspects of health utilization.”¹⁶³

Furthermore, experts are optimistic that this intervention has the potential to meet this unmet need. As one clinical expert stated, “A medication that has few side effects, efficacy, and is not cost prohibitive has the potential to improve both the quality of life and duration of transplant-free survival for this patient population.”¹⁶³ Expert support for this intervention stemmed from both the promising data seen so far in clinical trials, and from the underlying theory of using sildenafil for this condition. One clinical expert stated, “Studies in other human disease states and the underlying mechanism sildenafil, combined with the physiologic condition post-Fontan are promising that the medication will have a meaningful clinical benefit.”¹⁶³

Because the drug is administered orally and can be taken by the patient at home, most experts do not expect the addition of this drug to the physician armamentarium to be particularly disruptive to infrastructure or patient management models. Some experts noted that if the agent is effective, less care may be required of the health system (e.g., fewer physician visits or hospitalizations), but because the target patient population is small, this isn’t likely to translate into major changes for the overall health care system.

Because no other pharmacotherapies have been shown to be effective for this purpose, and given that sildenafil has been on the market and used off-label for a variety of conditions for quite some time, experts thought that both clinicians and patients will readily accept this intervention. However, almost all experts noted that the drug is expected to be very expensive if used in this off-label capacity, which may pose a barrier to uptake. While some experts suggested that cost-effectiveness studies (e.g., showing sildenafil can reduce hospitalization costs) may improve payers’ willingness to reimburse its use, until such studies can be completed, experts thought, the cost of sildenafil would be prohibitively high for this condition.

Percutaneous Annuloplasty (Carillon Mitral Contour System) to Treat Functional Mitral Regurgitation

For patients with pharmacotherapy-refractory functional mitral regurgitation (FMR), surgical intervention is typically indicated.¹⁶⁶ However, current surgical techniques (e.g., valve repair, replacement) are associated with risk of morbidity and mortality, and many patients are ineligible for surgical intervention.^{166,167} If approved for marketing, this percutaneous annuloplasty intervention could offer the first minimally invasive intervention for this patient population.¹⁶⁷

Percutaneous annuloplasty attempts to replicate the functional effects of open surgical annuloplasty, a procedure in which a surgeon implants a rigid or semirigid ring to reinforce the valve's annulus (a fibrous tissue ring around the mitral valve opening that supports the valve leaflets).¹⁶⁸ Surgeons using percutaneous annuloplasty implant the device using catheters guided through the vasculature to the heart. The clinician guides the catheter from within the coronary sinus, a large vein located along the heart's outer wall between the left atrium and left ventricle, adjacent to the mitral valve.¹⁶⁸ In clinical trials, physicians have performed percutaneous annuloplasty on patients under general anesthesia to facilitate transesophageal echocardiography.¹⁶⁸

The Carillon[®] Mitral Contour System[™] (Cardiac Dimensions, Inc., Kirkland, WA) comprises a thin, flexible metal bridge or tether with a self-expanding anchor at each end.¹⁶⁸ The clinician delivers the device to the coronary sinus using a catheter inserted in the jugular vein at the neck. After securing the distal anchor within the coronary sinus, the physician places tension on the delivery catheter to reshape the mitral annulus and reduce the degree of mitral regurgitation (MR). If the tension does not sufficiently reduce MR, surgeons typically do not deploy the device. If tension is sufficient, the proximal anchor is released from the delivery catheter and secured in place, after which the delivery catheter is removed. This tension around the mitral valve annulus squeezes the mitral leaflets together to close the gap that may have developed due to heart enlargement.¹⁶⁸ According to the device manufacturer, the implantation procedure is "simple" and is often completed in less than an hour.¹⁶⁹

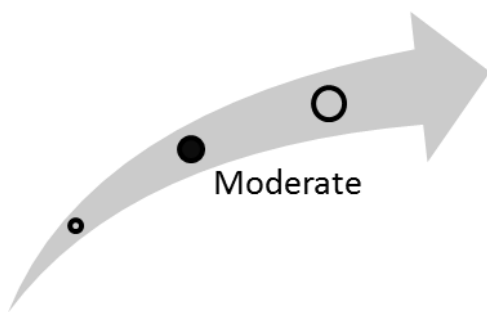
No ongoing clinical trials investigating this device are registered with the National Clinical Trials database in the United States. The manufacturer reports that the device is in two international trials, in South America and Europe.¹⁷⁰ In results of a 2010 trial of the Carillon device, which enrolled 53 patients, authors concluded: "At baseline, 94% of patients were NYHA [New York Heart Association class] III, EF [ejection fraction] was 28.4%, and LVEDD [left ventricular end-diastolic diameter] was 70mm. The MAE rate at 30-days for all 53 attempted patients was 1.9%. Reductions in 4 quantitative FMR measures ranged from 32-43% at 6 months for implanted patients. LVESV [left ventricular end-systolic volume] was reduced from 164±64 (baseline) to 142±52 (6 months) (p<0.01)."¹⁷¹ A 2009 trial of the Carillon device enrolled 48 patients, 30 of whom received the device. Eighteen patients did not receive the device because of access issues, insufficient acute FMR reduction, or coronary artery compromise. The major adverse event rate at 30 days was 13%; at 6 months, the degree of FMR reduction among five different quantitative echocardiographic measures ranged from 22% to 32%. Six-minute walk distance improved from a mean of 87 meters at baseline to 137 meters at 6 months after treatment (p<0.001). Quality of life, measured by the Kansas City Cardiomyopathy Questionnaire, improved by more than 20 points from baseline to 6 months (p<0.001).¹⁷²

This device is not yet approved for marketing in the United States, where it is limited to investigational use only.¹⁷³ In February 2009, the Carillon system received Conformité Européenne (CE) mark approval in Europe to treat FMR.¹⁷⁴

Clinical Pathway at Point of This Intervention

Although organic mitral valve regurgitation treatment is explicitly outlined by ACC/AHA guidelines, the optimal strategy for treating FMR is still debated.^{166,175} This controversy stems from a growing consensus that FMR arises from ventricular etiology, not from the valve itself, prompting questions about whether treatment should target valve or ventricular pathology.¹⁶⁶ For all patients with FMR, optimal medical management, including pharmacotherapies such as angiotensin-converting enzyme inhibitors, beta blockers, digitalis, diuretics, and vasodilators, is indicated.¹⁶⁶ For patients whose signs and symptoms recur despite these therapies or for asymptomatic patients who have left ventricular dysfunction, surgery is indicated.¹⁶⁶ Preferred surgical interventions for treating severe FMR include mitral valve replacement and mitral valve repair (e.g., annuloplasty, Alfieri correction).¹⁶⁶

Figure 9. Overall High Impact Potential: Percutaneous annuloplasty (Carillon Mitral Contour System) to treat functional mitral regurgitation



Experts commenting on this intervention generally agreed that the unmet need for a less invasive alternative to surgical mitral valve repair is important. However, expert uncertainty about the device's long-term safety and efficacy profiles indicate that more data are needed to determine whether this approach will fulfill its potential. Should the device be proven safe and effective, experts thought, it could reduce recovery time and hospital length-of-stay for patients, and they thought that the device would be readily adopted by clinicians and patients. Based on this input, our overall assessment is that this intervention is moderate within the high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.¹⁷⁶⁻¹⁸¹

Most experts agreed that the unmet need for a less invasive alternative to surgical mitral repair is important and may offer a treatment option for patients who are ineligible for surgery. However, some experts opined that because surgical mitral repair is already available, the unmet need that this intervention purports to address is somewhat incremental.

In terms of improving health outcomes, some experts suggested that this intervention might improve patient health by sparing them the morbidity and mortality that they would incur if they were to undergo surgical intervention. However, experts who formed their opinion of the device's efficacy based on trial data were less optimistic, stating that while the data are somewhat promising, more data are needed to clarify the device's long-term efficacy and safety profile. Experts also commented that for this procedure to diffuse, data comparing it to alternative therapeutic options (e.g., medical management, surgical intervention) would be necessary.

Experts thought that should this device become diffused, it has the potential to effect moderate changes to current health system operations, including shortening hospital stays and recovery time

for patients. While some experts suggested that this intervention would require less technical experience to perform than surgical mitral valve repair, other experts disagreed, stating that this intervention is likely to require significant training on the part of the clinician.

In general, experts thought that this intervention would be adopted by both clinicians and patients, because of the “less invasive nature of the procedure, probably lower complication rate, and relatively simplicity of the procedure compared to open surgical mitral valve repair,” along with the “probably shorter hospital stay and probably shorter recovery time.”¹⁷⁸ However, some experts suggested that this intervention may cause some contention between interventionists and cardiac surgeons.

Transcatheter Aortic Valve (CoreValve and Sapien) Implantation for Treatment of Severe Aortic Stenosis

The gold standard for treating aortic stenosis is open surgical replacement with a mechanical valve or a tissue valve obtained from cattle, pigs, or human cadavers.¹⁸² However, open-heart surgery requires cardiopulmonary bypass and is typically not an option for patients at high risk for surgical complications.¹⁸² Thus, manufacturers have developed minimally invasive approaches to valve replacement to extend the therapeutic benefit of aortic valve replacement to high-risk surgical patients.¹⁸²

Medtronic, Inc. (Minneapolis, MN), developed the CoreValve[®] System, which is being investigated for treating aortic stenosis in the United States.¹⁸³ The system is intended for use in patients who are not surgical candidates or who are at high surgical risk.¹⁸² The system features a porcine pericardial tissue valve mounted in a self-expanding, hourglass-shaped, nitinol-alloy mesh frame.¹⁸² The bioprosthetic valve is deployed using an 18-French diameter delivery catheter with a set of disposable catheter-loading components.¹⁸² According to the manufacturer, the implantation procedures lasts about 1–3 hours, and patients are typically sedated. The clinician guides a sheath into the heart, then threads a balloon catheter through the sheath into the heart. Once the balloon is positioned in the aortic valve, it is inflated, preparing the aortic valve for implantation of the CoreValve. Using imaging equipment, the clinician places the CoreValve over the diseased aortic valve. In some cases, the diseased valve is completely removed before placement of the CoreValve. The manufacturer claims that the CoreValve begins working immediately. The catheter is removed, and the incision is closed. The manufacturer states that the typical hospital stay following a transcatheter aortic valve Implantation (TAVI) procedure is 3–5 days.¹⁸⁴

CoreValve received Conformité Européenne (CE) mark for the CoreValve Percutaneous ReValving[™] System for treating high-risk patients in May 2007.¹⁸⁵ In September 2010, Medtronic received the CE mark for the CoreValve delivery system with AccuTrak[™] stability layer for TAVI.¹⁸⁵ Medtronic received an investigational device exemption for its CoreValve trial from FDA in October 2010 and has begun enrolling patients.^{185,186} In January 2012, the company announced that this pivotal trial had completed enrollment with more than 1,500 patients at 45 U.S. clinical sites.¹⁸⁷

In a May 2011 press release, Medtronic stated the following, regarding results from a 2011 meta-analysis of data from 2,156 patients with severe aortic stenosis who were treated with the CoreValve System: “The results demonstrate positive patient outcomes based on procedural success rate (97.8 percent), vascular complication rate (2.9 percent), one-month stroke rate (1.9 percent), one-month survival rate (93.8 percent) and one-year all-cause mortality rate from five registries (17.1 percent).”¹⁸⁸

Edwards Lifesciences, LLC (Irvine, CA), developed the Sapien[™] Transcatheter Heart Valve (THV) for potential use in patients with severe aortic stenosis who are at high surgical risk or who are not surgical candidates.¹⁸² The bioprosthesis features a bovine pericardial tissue aortic valve affixed within a balloon-expandable cobalt-chromium alloy frame.¹⁸² The bioprosthetic valves are available in 23 and 26 mm lengths.¹⁸² The RetroFlex[®] and RetroFlex II[™] delivery catheters are used to deploy the valve using femoral artery access, and the Ascendra[™] delivery system is designed to implant the valve via minimally invasive surgery using a transapical approach.¹⁸² Only the transfemoral approach has been evaluated by FDA for marketing approval at this time.¹⁸⁹

According to an informational guide published by the manufacturer, for Sapien THV implantation using the transfemoral approach, the patient is placed under general anesthesia. An incision is made in the patient’s groin, where the physician places a sheath in the femoral artery. A balloon catheter is used to stretch the aortic valve opening. The replacement aortic valve is placed

on the delivery system and crimped to allow insertion into the body through the sheath. Using fluoroscopy guidance, the valve and delivery system are inserted through the sheath and guided to the aortic valve. Once the new valve is positioned, the balloon is filled with liquid, expanding the new valve from its crimped mode to its functional mode. The valve is checked for proper function, the delivery system is removed, and the incision is closed. The manufacturer states that the valve begins working immediately. The procedure is conducted in 1–3 hours, and the average hospital stay for a patient undergoing the TAVI procedure is 2–6 days.^{190,191}

In November 2011, the manufacturer announced that FDA had granted it approval for the transfemoral delivery of the Sapien transcatheter aortic heart valve for treating patients who have severe, symptomatic aortic stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing comorbidities would not preclude the expected benefit from the procedure.¹⁹² The company also stated the following conditions of approval: “As part of this approval, FDA has requested the implementation of two substantial post-approval studies. One study will follow patients already enrolled in The PARTNER Trial, and the second study will track new U.S. patients. The company anticipates the second study will be incorporated into a new national patient registry.”¹⁹²

In an April 2011 press release, Edwards stated the following regarding results of the PARTNER trial, which were included in the FDA submission package:

In patients with aortic stenosis at high risk for surgery, transcatheter aortic valve replacement (TAVR) was non-inferior to surgical aortic valve replacement (AVR) for all-cause mortality at one year, 24.2 percent versus 26.8 percent, respectively. In addition, mortality at 30 days was lower than expected in both arms of the trial, with TAVR at 3.4 percent and AVR at 6.5 percent. The observed mortality in these AVR patients was lower than the thought risk of operative mortality of 11.8 percent... Both TAVR and AVR were associated with important but different peri-procedural hazards. The study demonstrated that major vascular complications and neurological events were more frequent with TAVR, while major bleeding and new onset atrial fibrillation were more frequent with AVR. Symptom improvement as measured by the New York Heart Association (NYHA) class and six-minute walk distance favored TAVR at 30 days and was similar to AVR at one year.¹⁹³

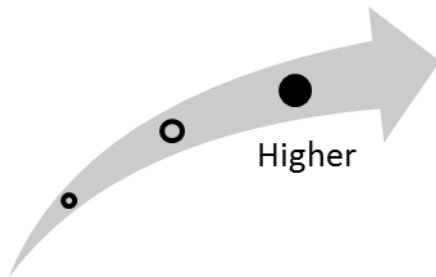
In May 2012, the U.S. Centers for Medicare & Medicaid Services (CMS) released a National Coverage Determination for TAVI, stating that CMS “covers transcatheter aortic valve replacement (TAVR) under Coverage with Evidence Development (CED)” when it the procedure is used for “the treatment of symptomatic aortic valve stenosis when furnished according to an FDA approved indication” and when certain conditions are met.¹⁹⁴

In November 2011, Reynolds reported a cost-effectiveness comparison between TAVR and open-heart aortic valve replacement among Cohort A (high-risk) patients in the PARTNER trial. The authors found that for transfemoral TAVR, procedural costs were substantially higher than those for open-heart aortic valve replacement (\$34,863 vs. \$14,451). However, overall treatment costs for the entire index hospitalization were somewhat lower for transfemoral TAVR than for open surgery (\$71,955 vs. \$74,452, $p=0.53$). The \$2,497 cost reduction in favor of transfemoral TAVR compared with open valve surgery was due to lower nonprocedural costs (\$31,192 vs. \$54,228), mainly because of a 6.2-day shorter length of stay in the transfemoral TAVR group (10.2 vs. 16.4 days, $p < 0.001$).¹⁹⁵

Clinical Pathway at Point of This Intervention

In patients with aortic stenosis, medical therapy is prescribed to alleviate symptoms, which include chest pain, shortness of breath, and fainting.¹⁸⁵ According to 2006 guidelines by ACC/AHA, aortic valve replacement is considered the surgical treatment of choice for most adults with severe aortic stenosis.¹⁹⁶ However, some patients are not candidates for surgical aortic valve replacement and therefore have a poor prognosis. TAVI is a new procedure intended to provide a less-invasive option for these patients, many of whom would have no treatment options otherwise.¹⁸⁵

Figure 10. Overall High Impact Potential: Transcatheter aortic valves (CoreValve and Sapien) implantation for treatment of severe aortic stenosis



Experts commenting on this intervention agreed that it would offer an important and likely safe and effective new treatment modality for patients who have no other medical or surgical treatment option. Experts expected that this intervention would improve patient health outcomes, and they thought an increase in patient volume and a shift in care setting (from outpatient to inpatient) would be seen as this intervention diffuses. Experts offered diverging opinions on whether this intervention would be particularly disruptive to health care infrastructure, but agreed that the intervention has the potential to both increase (in the short term) and decrease (in the long term) health care costs. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health system backgrounds, offered perspectives on the CoreValve technology.¹⁹⁷⁻²⁰³ Six experts, with similar backgrounds, offered perspectives on the Sapien technology.²⁰⁴⁻²⁰⁹ Two of these experts claimed potential conflicts of interest, because they both are involved in implanting these valves in their respective medical centers. These potential conflicts of interest are balanced by experts who did not claim conflicts of interests.^{204,209}

Experts reached a firm consensus that the unmet need that this intervention purports to address is extremely important, in light of the large number of patients who would be affected, and the fact that no other therapies are available for this population. As one clinical expert stated: “There is a large gap for certain patient populations. Patients currently deemed too high a risk for surgery have only a medical option [and] medical therapy has no impact on the natural history of the disease, thus mortality is high.”²⁰⁹ Furthermore, experts assert that this large patient population is growing as the population ages and as better techniques for identifying patients with aortic stenosis are developed.

Experts were optimistic about this intervention’s ability to meet the unmet need and improve patient health outcomes, mostly due to encouraging data from clinical trials, but also because no other options are available for this population. Some experts suggested that over time, this intervention may be extended to patient populations who are “less ill,” as well, although data on safety and durability of the procedure for this expanded patient population would need to be collected.

Experts were divided in their opinion on whether this technology would markedly disrupt current health care infrastructure and patient management models. While some experts stated that this intervention could be conducted in existing facilities, thereby not markedly disrupting current infrastructure, one clinical expert stated: “Starting a TAVR program...is a huge undertaking. It is not just adding another procedure, it is adding a whole new program to a medical center. The resource utilization is considerable. The program will put a significant strain on conventional resources and require an additional infrastructure to evaluate potential patients.”²⁰¹ One notable consequence of this intervention is the shift in care setting for patients who typically would only have been treated with medical therapy. Patient volume is expected to rise accordingly.

Experts thought that clinicians who would perform this procedure would readily accept this technology, considering that no other interventions are available for this patient population, but actual adoption may be slow, given that the procedure is likely to be rolled out only in selected centers at first. Experts also generally expected patients to accept this procedure, because it offers a therapeutic option where previously none existed and because the intervention is considered minimally invasive.

Experts were confident that this intervention would have significant impact on health care costs. First, because the device itself, as well as the deployment procedure are expensive. Second, because these patients would have been previously treated with medical therapy, cost increases with the implementation of this new intervention would be significant. Several experts noted that some costs associated with medically managing end-stage patients might go down (e.g., hospitalizations).

Transcatheter Mitral Valve Repair (MitraClip) for Treatment of Mitral Regurgitation

Although open surgical repair of the mitral valve is considered the gold standard treatment for mitral valve disease, some patients are not candidates for surgery because of their high risk for complications. Thus, there is an unmet need for an intervention that offers an alternative to open surgical mitral valve repair.

The MitraClip (Abbott Laboratories, Abbott Park, IL) device is intended to simulate the functional effects achieved by the Alfieri edge-to-edge surgical procedure, an open surgery repair technique used for treating MR.²¹⁰ In the Alfieri procedure, a surgeon sutures together the edges of the two opposing mitral valve leaflets at the center of the valve opening, leaving two smaller openings on either side that close more completely than a single large opening.²¹¹ The MitraClip device mimics this procedure by “clipping together” the mitral valve leaflets, rather than using sutures.^{210,212}

The MitraClip is an implantable, two-armed, flexible, metal clip, made of cobalt/chromium and covered in polyester fabric, that is intended to help the mitral valve close more completely, thereby potentially reducing MR.²¹³ The MitraClip system consists of the clip device, a clip-delivery system, and a steerable guide catheter.²¹⁴ To implant the device, the clinician inserts the guide catheter through the femoral vein into the heart and then, using the catheter and the clip-delivery systems, delivers and deploys the clip device.²¹⁴ The device is placed by advancing the guide catheter into the left atrium and positioning the opened clip over the mitral valve. The clip is advanced to the left ventricle, where its arms are closed, clamping the mitral valve leaflets together.²¹⁰ At this point, MR is assessed; if the change in MR is not satisfactory, the clip is repositioned.²¹⁰ The implantation procedure requires a transseptal puncture, which has been called a “crucial early step” in the procedure. The procedure is performed in a catheterization laboratory with fluoroscopy and echocardiographic guidance.²¹⁰ The manufacturer states that the procedure is performed under general anesthesia (but without the use of a heart-lung machine) and that recovery typically lasts from 1–3 days.²¹⁴

The MitraClip is not yet approved for marketing in the United States. Originally, the device was anticipated to be reviewed by FDA in 2011. In May 2011, the manufacturer issued a voluntary recall of the device in Europe, Australia, Singapore, and other countries where the device had been approved, because of issues with the delivery catheter’s tip. While the company resolved the issue and reintroduced the device in those countries, the recall prompted FDA to request additional information and analysis regarding the MitraClip, which the company provided.²¹⁵ The MitraClip is under evaluation in a phase III clinical trial in the United States.²¹⁶

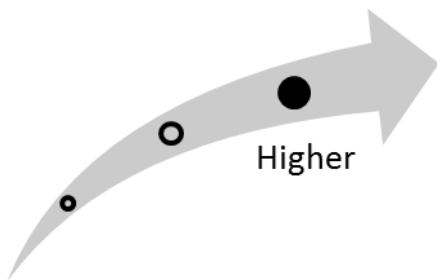
In a 2012 clinical trial of 78 patients with significant MR in whom the device was implanted, study investigators stated, “Seventy-eight patients underwent the MitraClip procedure. Their mean age was 77 years, >50% had previous cardiac surgery, and 46 had functional MR and 32 degenerative MR. MitraClip devices were successfully placed in 96% of patients. Protocol-predicted surgical mortality rate in the HRS and concurrent comparator group was 18.2% and 17.4%, respectively, and Society of Thoracic Surgeons calculator estimated mortality rate was 14.2% and 14.9%, respectively. The 30-day procedure-related mortality rate was 7.7% in the HRS and 8.3% in the comparator group ($p = \text{NS}$). The 12-month survival rate was 76% in the HRS and 55% in the concurrent comparator group ($p = 0.047$). In surviving patients with matched baseline and 12-month data, 78% had an MR grade of $\leq 2+$. [LV] end-diastolic volume improved from 172 ml to 140 ml and end-systolic volume improved from 82 ml to 73 ml (both $p = 0.001$). [NYHA] functional class improved from III/IV at baseline in 89% to class I/II in 74% ($p < 0.0001$). Quality

of life was improved ([SF-36] physical component score increased from 32.1 to 36.1 [$p = 0.014$] and the mental component score from 45.5 to 48.7 [$p = 0.065$]) at 12 months. The annual rate of hospitalization for congestive heart failure in surviving patients with matched data decreased from 0.59 to 0.32 ($p = 0.034$).²¹⁷

Clinical Pathway at Point of This Intervention

The preferred treatment for severe MR is surgical valve repair or replacement.^{217,210} ACC/AHA clinical guidelines recommend surgical mitral repair over mitral valve replacement in most patients, because the “valve is suitable for repair and appropriate surgical skill and expertise are available.”¹⁷⁵ If approved for marketing in the United States, the MitraClip would be positioned as a percutaneous alternative to surgical valve repair.^{217,210}

Figure 11. Overall High Impact Potential: Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation



Overall, experts commenting on this intervention thought that the MitraClip procedure has the potential to have a substantial impact on most parameters of the health care system, such as disrupting care models, increasing infrastructure and staffing requirements, shifting care setting, and requiring substantial clinician training; they were split on whether it would increase or decrease costs. Although several experts noted the need for longer-term safety data, experts generally believe this device has the potential to meet the need for minimally invasive interventions for treating MR. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this technology.²¹⁸⁻²²⁴ One clinical expert has performed nonfunded research with the company that developed the MitraClip. This potential conflict of interest was balanced by the perspectives of the remaining six experts who had no conflicts of interest.

Experts agreed that the unmet need for less invasive interventions for MR is important, based on both the prevalence of the disease and the risks that prevent some patients from undergoing open surgical repair. Although experts generally agreed that the underlying theory of replicating sutures with a device is sound, they were divided about whether this device would improve patient outcomes. Some experts, basing their opinions on early clinical data, posited that the device would be safer and offer a better quality of life for patients when compared with open surgery. However, several experts commented that the procedure might be associated with long-term risks, such as clotting or device malfunction, that will become clearer only after longer trials are completed. The clinical expert with research experience in this area stated, “The intervention can and does work, but in highly selected patients. Approximately 1/10 patients with MR are eligible for this procedure and approximately 70% of these selected patients will have a reasonably favorable outcome.”²²⁴

Experts' comments consistently concurred that the device has potential to affect the care model, treatment paradigm, and patient management. This intervention would be the first minimally invasive option for patients with MR and would provide an option for patients who are not candidates for open surgery. Second, because the procedure is minimally invasive and offers a faster recovery time, it has the potential to reduce the number of open surgeries performed, reduce use of cardiac care unit resources, and shorten hospital stays. Third, postoperative treatment plans are likely to be less complicated than for open surgeries.

Experts generally agreed that this intervention would affect care processes, including clinician training requirements, infrastructure needs, care setting, and staffing models. First, the transseptal puncture approach is considered to be a high-risk technique that would require substantial training of interventional cardiologists. The clinical expert experienced in this procedure stated that it "requires a highly skilled team that communicates well. Not every interventional cardiologist or echocardiographer will be able to perform this procedure."²²⁴ Second, staffing models would shift from surgical teams and the operating room to catheterization teams and the catheter and electrophysiology laboratories. Patient throughput would increase, and care associated with sternal incision and its subsequent risks would decrease. In terms of cost, most experts thought that despite the initial high cost of the device (\$31,000), overall costs associated with treating MR might ultimately decrease because of the device's potential to replace expensive open surgical procedures and reduce length of hospital stays.

Experts thought that patients would accept this intervention, primarily because of its minimal invasiveness, faster recovery time, and reduced potential for adverse events. Experts noted that patients who are contraindicated for open surgery would welcome a treatment option when they had none before. While a couple of experts thought that clinicians would be open to accepting this procedure, most thought some reluctance would be found in the medical community. First, some experts thought clinicians would be slow to adopt the intervention, because of the specialized training required to perform the procedure, especially until more and longer-term data become available. Second, because the device is "attempting to replace a gold standard, there may be resistance," one expert wrote. One health systems expert stated that this procedure is more likely to be adopted in "higher medical university centers and specialized surgery centers, because there will be appropriate skill sets and infrastructure available for this procedure. Smaller hospitals that do not have access to multiple cath labs and clinicians who do not have the skill set to perform this procedure might not be that inclined to adopt this intervention."

Experts thought high potential for controversy exists, mainly because of the ongoing "turf wars" between interventional cardiologists and surgeons but also because of the need for more clinical data and the risk associated with transseptal puncture.

Transcatheter Pulmonary Valve (Sapien) for Treatment of Congenital Pulmonary Valve Defects

Before the FDA approval of the Melody[®] Transcatheter Pulmonary Valve in January 2010 under humanitarian device exemption status, no minimally invasive alternatives to open surgical valve repair existed for patients with congenital pulmonary valve defects, and these patients had to undergo multiple open-heart surgeries over their lifetimes to address the problem.²²⁵ Therefore, percutaneous pulmonary valve implantation (PPVI) has the opportunity to address a significant unmet need. If approved for this indication, the Sapien[™] percutaneous pulmonary valve would be the second entrant to this market. The Sapien transcatheter pulmonic valve system is intended to serve a patient population with larger failed conduits than the Melody system because the valve (23 and 26 mm) and delivery systems (22 and 24 French [Fr] diameter) are available in larger sizes.^{226,227}

The Sapien Pulmonic Transcatheter Heart Valve system (Edwards Lifesciences, LLC, Irvine, CA) consists of a bovine pericardial valve sutured to a stainless steel stent and is delivered using the RetroFlex[™] transfemoral delivery system.^{228,229} The Sapien system serves a patient population with larger failed conduits because the valve (23 and 26 mm) and delivery system (22 and 24 Fr) are available in larger sizes than the Melody system.²²⁷

A search of the manufacturer's Web site did not reveal detailed instructions for the implantation procedure. However, a standard implantation technique for PPVI for right ventricular outflow tract (RVOT) defects has been described in the literature.²³⁰ In this technique, the procedure is performed via the femoral vein, under general anesthesia. After hemodynamic and angiographic assessment, a balloon-expandable stent is deployed in the homograft, and hemodynamic assessment and angiography are repeated. The femoral vein is dilated, and the sheath is inserted. The valve is crimped onto the appropriate balloon delivery system and delivered under fluoroscopic guidance. After valve implantation, gradient, pulmonary regurgitation, obstruction, and valve competence (without a wire) are assessed.²³⁰

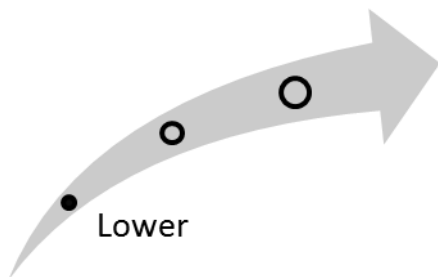
The safety of this device is being investigated in a clinical trial in the United States.²²⁹ In results of a 2011 trial of 36 patients with moderate to severe pulmonary regurgitation with or without stenosis, who received the Sapien valve in the pulmonary position, researchers stated, "Successful valve deployment was achieved in 33 of 34 attempts (97.1%). Valve migration occurred in 3 patients, with 2 requiring surgical retrieval; however, 1 patient underwent successful [periventricular] valve implantation. Further intraprocedure complications included pulmonary hemorrhage (n = 2), ventricular fibrillation (n = 1), and stent migration (n = 1). Pullback gradient across the conduit decreased from 26.8 ± 18.4 mm Hg to 11.7 ± 8.0 mm Hg ($p < 0.001$). The right ventricular/aortic pressure ratio decreased from 0.6 ± 0.2 to 0.4 ± 0.1 ($p < 0.001$). Peak Doppler gradient across the right ventricular outflow tract decreased from 41.9 ± 27.9 mm Hg to 19.1 ± 13.3 mm Hg ($p < 0.001$). At 6-month follow-up, all patients were alive. The number of patients with [NYHA] functional class I increased from 5 at baseline to 27 at follow-up. Pulmonary regurgitation was $\leq 2+$ in 97% of patients. Freedom from reintervention was 97% with 1 patient undergoing elective placement of a second valve due to conduit-induced distortion of the initial implant."²³¹ In the United States, the company intends to apply for a humanitarian device exemption from FDA.²²⁹ The device received Conformité Européenne (CE) mark approval for the pulmonic valve in May of 2010.²²⁹

Pricing for the device is not available; however, Medtronic Inc.'s Melody Transcatheter Pulmonary Valve system may provide a benchmark for the price of the Sapien system. The Melody valve and delivery device costs \$30,500, with procedural costs totaling about \$50,000.

Clinical Pathway at Point of This Intervention

Standard treatment for pulmonary valve dysfunction involves open-heart surgery to maintain or enhance blood flow from the right ventricle to the lungs. During the surgical procedure, three options are available to replace a failed RVOT: a mechanical valve, a bioprosthetic valve, or a homograft. Although durable, mechanical valves in the RVOT conduit are seldom used because of the need for life-long anticoagulation therapy to decrease the risk of thromboembolism.²³² A bioprosthetic valve replacement uses a porcine or equine pericardial leaflet valve supported in a plastic-metal framework and can be placed directly in the RVOT or integrated into a conduit.²³³ Most often, cardiac surgeons use a homograft consisting of a human cadaver aortic or pulmonary valve as a valved RVOT conduit.²³³ Over time, a conduit can fail for several reasons: a child with RVOT dysfunction outgrows the conduit,²³⁴ an aneurysm can form,²³⁵ or the valve can become insufficient,²³⁵ degenerate,²³⁶ or calcify.²³⁶ Bioprosthetic valves have been reported to require replacement after an average of 10 years.²³⁷

Figure 12. Overall High Impact Potential: Transcatheter pulmonary valves (Sapien) for treatment of congenital pulmonary valve defects



Although experts were optimistic about this intervention's ability to meet the need it purports to address, experts believe that the introduction and wide acceptance of the Melody valve somewhat tempers the Sapien valve's potential for high impact, as does the small size of the intended patient population. Because the intervention could reduce or delay the need for open-heart surgeries, this device could have a significant impact on multiple health system parameters by enabling patients to avoid open-heart surgery, moving a procedure from the surgical suite to catheter laboratory setting, reducing cost, and improving patient outcomes, but only for those patients who are not only served by the Melody valve. Based on this input, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health system backgrounds, offered perspectives on this intervention.²³⁸⁻²⁴⁴ Experts believe strongly that the need for minimally invasive pulmonary valve replacement is important, based on the risk associated with first-time or repeated open-heart surgery. Although the approval of the Melody valve addressed a significant portion of this unmet need, experts, especially those with clinical backgrounds, expressed the opinion that the unmet need that the Sapien purports to address (treating patients with larger conduits) is also important. That is, the expansion of the patient population who would be able to receive percutaneously implanted pulmonary valves represents an important unmet need. However, the fact that the manufacturer is seeking to request a humanitarian device exemption approval for the device (which are given in cases when a condition affects fewer than 4,000 patients) caused some experts to note that the intended patient population for this valve is small, which reduces the unmet need to some degree.

Furthermore, experts were somewhat confident that this implant would improve health outcomes, based on the success of the Melody valve, experience with Sapien in the aortic position,

and trial data to date. Experts are optimistic that this valve has the potential to both improve quality of life for patients and to delay the need for surgery for several years, which ultimately could reduce the number of surgeries a patient must undergo over a lifetime.

For the expanded patient population that the Sapien is intended to treat, experts expect this intervention to affect their care in a way similar to the way the Melody valve did for its target population. That is, patients would likely experience shorter recovery times, shorter lengths of stay in hospitals, less need for aftercare, and a shift in care setting from the operating room to the interventional laboratory. However, because of the experience accumulated with the Melody valve, experts did not think the same marked disruption that was seen when centers were first trying to implement the Melody procedure would occur with the Sapien device. Most experts expect that, given the success of the Melody valve, most patients and clinicians would readily accept this procedure.

Experts anticipated that this intervention would reduce costs of care associated with congenital pulmonary valve defects because it would likely be less expensive than open surgery, and length of stay would be shorter than open surgery. If the valve significantly delays the need for repeated open-heart surgeries, financial burden would also be reduced over the lifetime care of the patient.

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